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PNEUMONIA IN INFANTS AND CHILDREN

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IN THE six months ending June 1, 1939, a study of pneumonia in infants and children was made at the Children's Hospital of Michigan. In this period 630 patients were observed from the point of etiology and the effects of specific treatment with sulfapyridine and antipneumococcus rabbit serum. Of these, 248 were treated with sulfapyridine, 106 were treated with serum, and 276 received no specific treatment.

The diagnosis of pneumonia was made by the usual classical points in the history and from physical signs. Ninety per cent of the patients had an x-ray examination of the lungs as an additional check. In 10 per cent the x-rays failed to confirm the diagnosis, making it difficult to distinguish between pneumonia and severe bronchitis; however, the clinical course of all these patients substantiated the original opinion. No attempt was made to distinguish between types of pneumonia except on an etiological basis. The return of the temperature to a normal level was the usual criterion of cure of the pneumonia. A small number of infants with pneumonia had no fever during the course of the disease, and the criterion of cure in this group was the disappearance of physical signs from the lungs. Most patients had at least one additional x-ray of the lungs, but this could not be accepted as a proof of cure as the time of this examination was so variable.

The method employed for determining the causative organism follows: A deep pharyngeal swab was immediately placed in a centrifuge tube containing 2 to 3 c.c. of sterile human ascitic fluid, and the tube was incubated at 37° C. for three hours; the swab was removed and the tube centrifuged at moderate speed for five minutes; the supernatant fluid was discarded and a loopful of the sedi-

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ment placed on a slide to which was added appropriate "mixtures" of pneumococcus typing serum; the slide was examined microscopically for pneumococcal capsular swelling (Quellung phenomenon). If no organisms exhibiting capsular swelling were found, a loopful of the sediment was cultured on a blood agar plate. The entire procedure was repeated the same day or on successive days until it seemed reasonably certain that the pneumococcus could be excluded as the causative organism. It was possible to confirm this method of typing in certain cases. The presence of the same organism in a blood culture served as a valuable check although positive blood cultures are rarely found in pneumonia of infants and children. A culture of the same organism from the pleural fluid enabled us to check the results of typing in some cases. Direct culture of the lungs from fatal cases was occasionally a method of confirming the throat typing. The rapid lowering of the temperature following administration of type-specific antipneumococcus serum is suggestive evidence for the accuracy of the typing. The presence of more than one type of pneumococci in the throat was occasionally encountered, which made the decision as to the etiological type even more difficult. Previous experience has shown that certain types of pneumococci, notably Types VI and XIX, may be normal inhabitants of the throat in children, but in many instances one could do little more than hazard a guess as to the etiologic type. Direct puncture of the lungs was not attempted in any of these patients. Table I shows the distribution of the twelve types of pneumococci most frequently found this season in Detroit and the incidence of the other types and other etiologic organisms.

TABLE I

ETIOLOGY OF PNEUMONIA—DEC. 1, 1938, TO JUNE 1, 1939

CAUSATIVE ORGANISM	NUMBER OF INFANTS (0 TO 2 YR.)	NUMBER OF CHILDREN (2 TO 12 YR.)
Pneumococcus Type I	11	68
III	14	5
IV	15	6
V	7	9
VI	33	16
VII	4	11
XIV	38	15
XV	20	9
XVI	9	12
XVIII	23	10
XIX	67	12
XXIII	14	10
Other types of pneumococci	79	21
Mixed types of pneumococci	40	15
Hemolytic streptococcus	21	10
Staphylococcus	5	1
Totals	400	230

It was desired to select the method of treatment for each patient in rotating sequence, but this plan could not be followed exactly. From

previous experience, it seemed inadvisable to use specific serum after the sixth day of the disease, and this excluded some patients from this plan of treatment. Serum for specific treatment was not available for all thirty-two types of the pneumococcus. On certain occasions the supply of sulfapyridine or specific serum was exhausted. Sulfapyridine was purposely given some patients late in the course of the disease, even beyond the time when specific serum is considered to be of benefit.

Table II shows the average duration of the pneumonia at the time of admission to the hospital. It may be seen that the groups are readily comparable as far as this factor is concerned.

TABLE II

AVERAGE DURATION OF PNEUMOCOCCUS PNEUMONIA AT ENTRY

INFANTS (0 TO 2 YR.)		CHILDREN (2 TO 12 YR.)	
	All Patients		
Treated	3 days (av. dev., 1.4 days)	Treated	3 days (av. dev., 1.4 days)
Untreated	3 days (av. dev., 1.5 days)	Untreated	3 days (av. dev., 1.5 days)
	Patients Ill Less Than 5 Days at Entry		
Treated	2.5 days (av. dev., 1 day)	Treated	2 days (av. dev., 1 day)
Untreated	3 days (av. dev., 1 day)	Untreated	2 days (av. dev., 1 day)

The late administration of sulfapyridine to some patients is reflected in Table III, showing the average duration of the pneumonia at the start of treatment, where the average in patients under 2 years of age was six days for the sulfapyridine compared with three days for the serum with a corresponding wide variation in the average deviation.

TABLE III

AVERAGE DURATION OF PNEUMOCOCCUS PNEUMONIA AT START OF TREATMENT

INFANTS (0 TO 2 YR.)		CHILDREN (2 TO 12 YR.)	
	All Patients		
Sulfapyridine	6 days (av. dev., 3 days)	Sulfapyridine	4 days (av. dev., 2 days)
Serum	3 days (av. dev., 1 day)	Serum	4 days (av. dev., 1 day)
	Patients Ill Less Than 5 Days at Start of Treatment		
Sulfapyridine	4 days (av. dev., 1 day)	Sulfapyridine	3 days (av. dev., 1 day)
Serum	3 days (av. dev., 1 day)	Serum	3 days (av. dev., 1 day)

The same feature of the late administration of sulfapyridine may be noted in the duration of the pneumonia with an average difference of three days in the sulfapyridine and serum-treated groups. The duration of the pneumonia is noticeably lengthened in the untreated groups, although the average deviation is quite wide (Table IV).

The fatality rate of pneumonia was so low in the untreated group this year compared with other years that evaluation of specific treat-

TABLE IV

AVERAGE DURATION OF PNEUMOCOCCUS PNEUMONIA (ALL DEATHS EXCLUDED)

INFANTS (0 TO 2 YR.)		CHILDREN (2 TO 12 YR.)	
All Patients			
Treated with sulfapyridine	8 days (av. dev., 3.7 days)	Treated with sulfapyridine	6 days.(av. dev., 2 days)
Treated with serum	5 days (av. dev., 2.1 days)	Treated with serum	5 days (av. dev., 1.3 days)
Untreated	12 days (av. dev., 5 days)	Untreated	10 days (av. dev., 3.5 days)
Patients Ill Less Than 5 Days at Start of Treatment			
Treated with sulfapyridine	6 days (av. dev., 1.7 days)	Treated with sulfapyridine	5 days (av. dev., 1 day)
Treated with serum	6 days (av. dev., 2 days)	Treated with serum	5 days (av. dev., 1 day)
Untreated	12 days (av. dev., 5 days)	Untreated	9 days (av. dev., 3 days)

ment is difficult. Obviously the disease in infants and children in Detroit was milder than in other years. Table V shows the observed fatality rate in this group of patients.

TABLE V

FATALITY RATE IN PNEUMOCOCCUS PNEUMONIA

INFANTS (0 TO 2 YR.)				CHILDREN (2 TO 12 YR.)			
	CASES	DEATHS	PER-CENTAGE		CASES	DEATHS	PER-CENTAGE
All Patients							
Treated with sulfapyridine	138	6	4.3	Treated with sulfapyridine	110	1	0.9
Treated with serum	52	6	11.5	Treated with serum	54	1	1.8
Untreated	174	22	12.6	Untreated	102	3	2.9
Excluding Deaths in Patients Ill Over 5 Days at Entry, Ill More Than 5 Days at Start of Treatment, and Deaths in Less Than 24 Hours After Entry							
Treated with sulfapyridine	137	5	3.6	Treated with sulfapyridine	109	0	0
Treated with serum	50	4	8.0	Treated with serum	53	0	0
Untreated	167	15	8.9	Untreated	101	2	1.9

Empyema was such a rare complication of pneumococcus pneumonia that comparative statistical analysis of its occurrence in treated and untreated cases could not be made. There were 7 patients with empyema under 2 years of age, and 15 over 2 years. Only one patient in each age group developed the empyema after receiving specific treatment. The remaining 20 had signs of empyema on entry to the hospital. Specific serum was given to 6 of these patients without appreciable alteration of the course, for 5 required surgical drainage. Sulfapyridine was given to 7 patients with empyema; 4 of them required only one or more pleural taps to relieve the collection of fluid, and 3 had surgical treatment in the form of closed drainage. There was only one death in this group of 22 patients.

The use of specific treatment seemed to have a definite effect in reducing complications other than empyema, as shown in Table VI.

TABLE VI

COMPLICATIONS IN PNEUMOCOCCUS PNEUMONIA: EFFECT OF SPECIFIC TREATMENT

COMPLICATIONS	PATIENTS			
	TREATED		UNTREATED	
Meningitis	0	(0%)	4	(0.2%)
Mastoiditis	2	(0.8%)	12	(4.3%)
Suppurative otitis media	30	(10.8%)	56	(20.2%)

When sulfapyridine was first available, little was known about the optimal dose or blood level for children. Doses varied from 0.75 to 2.0 gr. per pound each 24 hours, and average blood levels of free sulfapyridine varied from 2 to 20 mg. per cent. It has been suggested[1] that 4 mg. per cent is the optimal blood level for adults; so with this in mind, an attempt was made to correlate the average blood level with the duration of the pneumonia after treatment was instituted. The average of 4 mg. per cent was chosen as the dividing line for the two groups of patients. It may be readily seen in Table VII that, except for the patients under 2 years of age whose treatment was started on or before the fifth day of the disease, there is little difference in the average duration of the pneumonia for either high or low average blood values of free sulfapyridine.

TABLE VII

RELATION OF DOSE AND BLOOD LEVEL OF FREE SULFAPYRIDINE TO DURATION OF PNEUMOCOCCUS PNEUMONIA

INFANTS (0 TO 2 YR.)

Treatment Started On or Before 5th Day			*Treatment Started After 5th Day*		
	0 TO 4 MG. % AV. 3 MG. %	OVER 4 MG. % AV. 9 MG. %		0 TO 4 MG. % AV. 3 MG. %	OVER 4 MG. % AV. 9 MG. %
Average dose:	1.3 gr./lb.	1.5 gr./lb.	Average dose:	1.25 gr./lb.	1.6 gr./lb.
Average duration:	2.8 days	1.9 days	Average duration:	3 days	2.8 days

CHILDREN (2 TO 12 YR.)

Treatment Started On or Before 5th Day			*Treatment Started After 5th Day*		
	0 TO 4 MG. % AV. 3 MG. %	OVER 4 MG. % AV. 8 MG. %		0 TO 4 MG. % AV. 3 MG. %	OVER 4 MG. % AV. 8 MG. %
Average dose:	1 gr./lb.	1.25 gr./lb.	Average dose:	1 gr./lb.	1.25 gr./lb.
Average duration:	1.6 days	1.3 days	Average duration:	1.5 days	1.5 days

Hemolytic streptococcus pneumonia occurred in 5 per cent of the patients. All deaths were in patients under 2 years of age, and the fatality rate was 29 per cent. Both sulfanilamide and sulfapyridine

were used for treatment in some of these patients. Sulfapyridine seemed to be equally as effective as sulfanilamide in bringing about cessation of the disease.

The staphylococcus was found as the cause of pneumonia in only 6 patients. Five of these were under 2 years of age, and the fatality rate was 100 per cent in this small group. In all of the fatal cases the patients received intensive treatment with sulfapyridine, and blood levels varying from 12 to 20 mg. per cent of free sulfapyridine were maintained. An empyema developed before death in each of the fatal cases, and the staphylococcus was obtained in pure culture from the empyema fluid.

Toxic reactions from sulfapyridine similar to those from sulfanilamide have been described.[2, 3] In addition, hematuria following the use of sulfapyridine has been observed.[4] Certain toxic reactions seen with sulfanilamide, such as hyperpnea and lowering of the CO_2 content of the blood and other chemical changes described,[5] have not been observed with sulfapyridine by Hartmann.[6] Table VIII shows the toxic reactions encountered in 248 patients treated with sulfapyridine. Nausea and vomiting were the most troublesome, but it was rarely necessary to withdraw the drug completely for relief of these symptoms. In patients under 2 years of age, the difficulty of administering fluids orally was interpreted as nausea. No special note was made of the occurrence of cyanosis as a toxic reaction. It was thought that the difficulty of distinguishing cyanosis due to the drug from cyanosis accompanying the pneumonia prohibited accurate observations. During the last three months of the study estimations of methemoglobin and sulphemoglobin were made according to the method of Evelyn and Malloy[7] in the blood of patients receiving sulfapyridine. The amounts of methemoglobin and sulphemoglobin found were too small to have any

TABLE VIII

TOXIC REACTIONS TO SULFAPYRIDINE IN 248 PATIENTS

REACTION	PERCENTAGE OF CASES
Nausea	
Infants (0 to 2 yr.)	50
Children (2 to 12 yr.)	10
Vomiting	10
Methemoglobin (125 patients)	
0 to 0.5 gm.	28
0.5 to 1 gm.	42
1 to 2 gm.	28
2 to 2.5 gm.	2
Sulphemoglobin (125 patients)	
0	95
0 to 1 gm.	5
Hemolytic anemia	0
Leucopenia	0
Rashes	0
Fever	0
Hematuria	0

special significance in most of the patients. No attempt was made to restrict the intake of fluids to attain a higher blood concentration of free sulfapyridine, which may have some bearing on the absence of hematuria in the patients who received the drug.

The usual plan of treatment for sulfapyridine was to administer the estimated full dose each 24 hours, to maintain it about 48 hours beyond the return of the temperature to normal, and then to continue on half the dose for 2 to 3 days before complete cessation. Recently two other plans of treatment were tried. The first of these was to estimate a dose of 1 grain per pound and administer this amount in a single dose without further administration. However, in most cases, it was found necessary to give added amounts 2 to 3 days later to reduce the temperature to normal. The second plan was to give the drug for only 48 hours, basing the dose on amounts equal to 1 grain per pound each 24 hours, preceded by an initial dose of 0.25 grain per pound. This plan was successful in most of the cases when treatment was started before the fifth day of the disease. However, in patients with pneumonia of more than 5 days' duration, it is advisable to continue administration of the drug 2 to 3 days beyond the point at which the temperature becomes normal. As far as can be determined from this study, sulfapyridine has been equally effective against all types of the pneumococcus.

No reactions were observed other than an occasional moderate chill or febrile response following the injection of specific antipneumococcus rabbit serum. The serum, diluted with physiologic saline solution, was administered intravenously in all cases. It was usually given in three or four divided doses as recommended by the manufacturer. Serum sickness was rarely observed following administration of the serum. With the exception of two patients who had Type XVIII pneumococcus pneumonia and received specific serum, the response to all the other types of serum which were given (Types I, V, VII, VIII, XIV, XV, XVI, XVIII, XIX, and XXIII) was equally effective. It has been suggested[8] that the two cases of Type XVIII pneumonia represented an unnumbered type above XXXII which has properties of cross-agglutination with a true Type XVIII.

SUMMARY AND CONCLUSIONS

Data on 630 patients with pneumonia have been presented. Of these patients, 248 were treated with sulfapyridine, 106 were treated with specific antipneumococcus rabbit serum, and 276 served as controls and received no specific treatment.

The fatality rate of untreated pneumococcus pneumonia in infants and children has been low for the season of 1938-1939 in Detroit, and the disease has followed a milder course than in previous years.

Specific treatment with both sulfapyridine and serum apparently reduced the total duration of the pneumonia and the fatality rate.

Specific treatment lowered the percentage of complications of pneumococcus pneumonia, such as meningitis, mastoiditis, and suppurative otitis media.

Although definite statistical proof is lacking, the optimal blood concentration of free sulfapyridine is recommended as 4 mg. per cent or above.

The incidence of empyema following pneumococcus pneumonia has been low for the cases studied this season, which offers further suggestion that the disease has been milder than in previous years.

The incidence of hemolytic streptococcus pneumonia has been low in the cases studied, and the fatality rate in untreated patients was relatively low. Evidence at hand suggests that sulfapyridine is as effective as sulfanilamide for treating this type of pneumonia.

Staphylococcus pneumonia occurred infrequently in this group of patients. Sulfapyridine had no beneficial effect on the course of the staphylococcus pneumonia in this group.

Toxic manifestations of sulfapyridine have been infrequent and mild. Neither hemolytic anemia, leucopenia, nor hematuria was observed. It is suggested that the maintenance of an adequate fluid intake may have some connection with the absence of such toxic reactions. In our experience, sulfapyridine appears to have fewer toxic reactions than sulfanilamide.

Sulfapyridine was equally effective in treating pneumonia caused by any of the 32 types of the pneumococcus.

Specific serum for the types available was equally effective, except for two cases of Type XVIII pneumococcus pneumonia which may not have been a true Type XVIII but a closely related unnumbered type above XXXII.

We wish to thank the Lederle Laboratories, Inc., Pearl River, N. Y., for supplying the specific antipneumococcus rabbit serum, and Merck & Company, Inc., Rahway, N. J., for furnishing the supply of sulfapyridine.

REFERENCES

1. Marshall, E. K., Jr., and Long, P. H.: J. A. M. A. **112:** 1671, 1939.
2. Flippin, H. F., Lockwood, J. S., Pepper, D. S., and Schwartz, L.: J. A. M. A. **112:** 529, 1939.
3. Barnett, H. L., Hartmann, A. F., Perley, A. M., and Ruhoff, M. B.: J. A. M. A. **112:** 518, 1939.
4. Southworth, H., and Cooke, C.: J. A. M. A. **112:** 1820, 1939.
5. Hartmann, A. F., Perley, A. M., and Barnett, H. L.: J. Clin. Investigation **17:** 465, 1938.
6. Hartmann, A. F.: Personal communication.
7. Evelyn, K. A., and Malloy, H. T.: J. Biol. Chem. **126:** 655, 1938.
8. Malcolm, W. G., The Lederle Laboratories, Inc., Pearl River, N. Y.: Personal communication.

LOCALIZED BULLOUS EMPHYSEMA ASSOCIATED WITH PNEUMONIA IN CHILDREN

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ABOUT two decades ago, a number of reports appeared in the literature dealing with the frequent occurrence of so-called "annular" shadows in roentgenograms of chests of adult patients with pulmonary tuberculosis. Up to that time, these had usually been diagnosed as "silent" intrapulmonary cavities, but it had become obvious that this interpretation was incorrect. As far back as 1917, Fishberg[1] discussed the importance of differentiating between tuberculous cavities within the lung parenchyma and abnormal, air-filled spaces within the thorax, which he considered were localized and interlobar pneumothoraces. A few years later, Sampson, Heise, and Brown[2] pointed out that annular or ringlike shadows, varying in shape, were seen in normal or mildly infiltrated lung fields in 50 (11.8 per cent) of 423 consecutive cases admitted to Trudeau Sanatorium. They stated that these shadows did not represent intrapulmonary cavities, but were due to interlobar or localized pneumothoraces or hydropneumothoraces. Amberson[3] concluded that pleural annular shadows were realities which had to be differentiated from intrapulmonary cavity shadows. Sergent[4] questioned the existence and, moreover, the frequency of so-called "silent" cavities, unless autopsy proof could be obtained to substantiate their presence. The true nature of the abnormality which produced these "annular" shadows began to be realized after Miller[5] published his results of a study of the human pleura pulmonalis in its relation to the blebs and bullae of emphysema. He described a bleb as a "subpleural emphysema," which forms as a result of the rupture of the wall of an alveolus, allowing air to escape into the areolar layer of the pleura. The air then tracks beneath the pleura in a manner similar to the formation of a dissecting aneurysm along the wall of an artery. Its extension may be arrested where the septa, which mark out a secondary lobule, join the pleura; or it may extend over a number of secondary lobules. If the alveoli are dilated and atrophy and rupture of the alveolar walls take place, a bulla is formed which communicates with a bronchiole or a larger division of the bronchial tree. The bleb which bulges on the surface of the lung in life is practically emptied of its air when respiration ceases, and at necropsy, an area of loose pleura which slides freely over the lung marks its location. The pleura over a bulla is not movable, and the underlying space gives

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the impression of an air-filled cavity. Miller wondered if some of the "annular shadows" and "small pneumothoraces" might not be blebs.

Experimentally, Laurell[6] produced bullous emphysematous spaces by inflating excised calves' lungs and showed histologically that there was a surrounding zone of atelectatic alveoli due to pressure of the air-filled space, which was seen as a ringlike shadow in the roentgenogram. Hayashi[7] and Fischer-Wasels[8] called attention to the formation of emphysematous spaces, which they called valve-vesicles, as a result of scar tissue due to a small localized inflammatory process, particularly tuberculosis, in the apices of the lungs in adults. Kjaergaard[9] described a case of simple emphysematous valve-vesicle without the presence of scar tissue, with rupture of the pleura causing spontaneous pneumothorax in an apparently healthy person. Jäderholm[10] noted the occurrence of bullous emphysema at the base of the left lung in a boy 18 years old, who had pneumonia. Miller[11] found a large emphysematous bulla which had been mistaken for a tuberculous cavity in a negro man, 66 years old. Freedman[12] observed five patients whose chest roentgenograms showed evidence of bullous emphysema. Of four who came to autopsy, in one an incorrect diagnosis of a tuberculous cavity had been made. Four were adults, and one was a male infant, 7 weeks old, whose lungs showed some atelectasis and emphysema with bleb formation in the right apex; none of them were associated with pneumonia. Duken,[13] Vollmer,[14] Kleinschmidt,[15] and Zarfl[16] used the term "pneumatocele" to designate large intrathoracic air-containing spaces in children. Peirce and Dirkse[17] have also employed this designation more recently for localized bullous emphysema; and they stress the fact that most so-called "cystic" lesions of the lung are not congenital but acquired. Lereboullet, Lelong, and Bernard[18] reported the presence, in the chest roentgenogram of a 4-month-old boy, recovering from bronchopneumonia, of an intrapulmonary bullous emphysematous space which remained unchanged for two and a half months. It then became progressively smaller until a month later it was not discernible any more. Under the heading "aputrid pulmonary necrosis," Kessel[19] described the finding of definite cavities in chest roentgenograms of adults at the time of pneumonic resolution, without the production of symptoms. These decreased in size and disappeared at the end of about two weeks. Five of the patients who showed what was interpreted as cavities recovered, but of three who came to autopsy and showed anatomic and histologic evidence of aputrid necrosis, no roentgenograms were available. The roentgenographic reproductions fit in very well with the appearance of localized bullous emphysema.

In the past six years we feel we have observed nineteen typical instances in which localized emphysematous air spaces have been associated with pneumonia in children. In most of these there was some

degree of pleurisy, which was often quite localized in the region containing the bullous emphysema. Two of the children had empyema, and two others developed pneumothorax, resulting from rupture of the pleura over the bullous emphysematous space.

The typical appearance of localized bullous emphysema in the roentgenogram consists of a thin, rather sharply defined, smooth shadow, almost like a white pencil line, surrounding an air-filled space of decreased density in which lung markings are diminished or absent. By means of stereoscopic, lateral, and oblique roentgenograms, one can demonstrate that the emphysematous spaces in the lung are spheroid, ovoid, or loculated. Occasionally they contain a small amount of fluid and show a straight line fluid level in the upright position, as occurred in Cases 4, 11, 13, 16 and 17. They do not persist but vary in size from time to time until they disappear. The shortest period over which one was visible was seven days, and the longest, in a case now being followed in which the shadow has persisted, for 10 months. He is entirely well clinically (Case 15). It has not been possible to follow one other patient, but in the remaining seventeen, roentgenograms taken at intervals show eventual complete clearing.

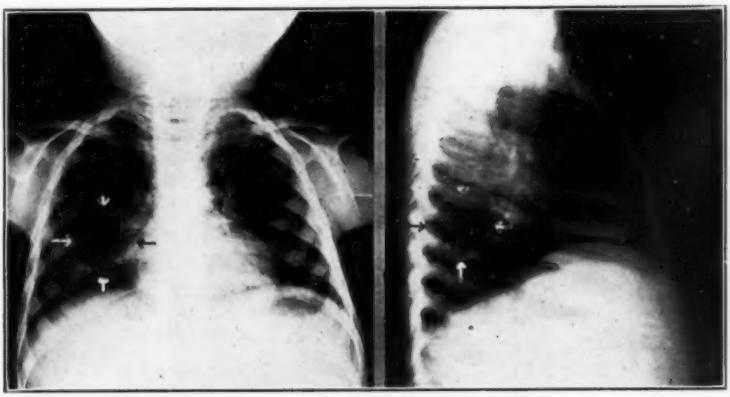

Fig. 1. Fig. 2.

Fig. 1.—Case 1, Aug. 31, 1932. There is a rounded area of diminished density with a thin dense margin in the right lower lung. This does not contain any fluid, and there is very little infiltration in the surrounding lung.

Fig. 2.—Case 1, Aug. 31, 1932. Direct lateral view showing that the area of diminished density is spherical and situated posteriorly in the right lower lobe.

CASE REPORTS

CASE 1.—M. G., male, 2 years old, was first seen Aug. 15, 1932. There was a history of cough for about six weeks, more marked for the first two weeks, when it was accompanied by fever. He had lost his appetite and had become weak. He was a poorly nourished, pale, and irritable boy. Physical examination showed pneumonia at the base of the right lung; the pneumonia soon disappeared, and the boy was discharged well Sept. 9, 1932, after he had been afebrile for three weeks. He remained well until Oct. 15, 1932, when he developed pertussis. He recovered after the usual

course but was readmitted Oct. 22, 1934, after he had been coughing and had had fever for four days. There were signs of pneumonia involving the left lower lobe. The temperature dropped to normal by crisis on Oct. 28, 1934, and he was well when last seen Nov. 16, 1934.

Fig. 3.

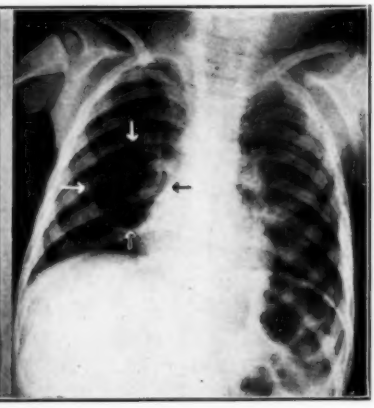

Fig. 4.

Fig. 3.—Case 1, Aug. 31, 1932. Right anterior oblique view, again demonstrating the transparent area and also the small associated pleural exudate.

Fig. 4.—Case 1, Oct. 27, 1932. There has been some increase in size of the area of diminished density, although the child remained symptom-free. Note the absence of a fluid level and the complete clearing of the adjacent lung.

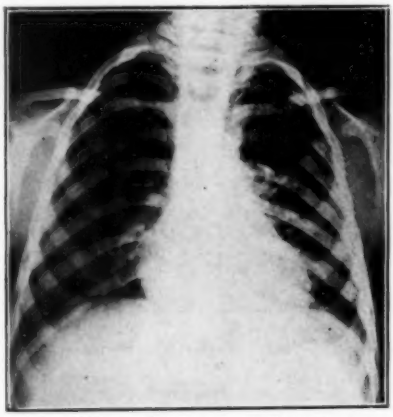

Fig. 5.—Case 1, Nov. 16, 1934. Follow-up roentgenogram, showing no residual changes at the base of the right lung.

Roentgenologic Examination.—On Aug. 15, 1932, there was consolidation involving the lower portion of the right lung. Ten days later most of this had cleared, but there was a rounded area of diminished density 3.2 cm. in diameter, situated in the lower portion of the right lung, reaching almost as far down as the dome of the diaphragm. The margins of this area were clear-cut and thin. On Aug. 31, 1932, posteroanterior, right and left oblique, and direct lateral films showed the area of diminished density to be the same in size as it was six days before and definitely proved that it was spherical. It was situated superficially in the posterior portion of

the lower lobe. There was also a small pleural exudate which reached a maximum width of 4 mm. (Figs. 1, 2, and 3). By Oct. 27, 1932, the area had become larger and had a diameter of nearly 4 cm. Its margins were even thinner than before, and all the surrounding infiltration had disappeared (Fig. 4). At no time did it contain any fluid. On May 5, 1933, no abnormality could be found. On Oct. 28, 1934, there was consolidation involving the left lower lobe. There was no evidence of an area of diminished density in the right lung. This pneumonia had practically cleared by Nov. 16, 1934 (Fig. 5).

CASE 2.—R. H., male, 7 years old, was admitted Jan. 6, 1934. He had been in the Alexandra Hospital since Nov. 13, 1933, where he had pneumonia at the right base and developed fluid in the right side of the chest. On Dec. 10, 1933, 250 c.c. of serous fluid were aspirated, and on Dec. 18, 1933, 8 c.c. of similar fluid were removed. No organisms were found in smears or culture. On Jan. 5, 1934, thoracentesis yielded no fluid. There were diminished movement, diminished breath sounds, and increased vocal resonance over the lower half of the right side of the chest. On Jan. 10, 1934, bronchoscopic examination showed some edema of the bronchus to the right lower lobe at its opening, but this had lessened by Jan. 17, 1934. Smears of a bronchoscopically aspirated specimen showed a few gram-positive cocci resembling pneumococci, but no acid-fast organisms. A guinea pig inoculated with pleural fluid showed no tuberculosis. Stomach washings revealed no tubercle bacilli. The boy had slight fever during the first week after admission, the highest recorded being 101° F. He was discharged after an uneventful recovery on April 30, 1934. Mantoux test (1:1,000) was positive.

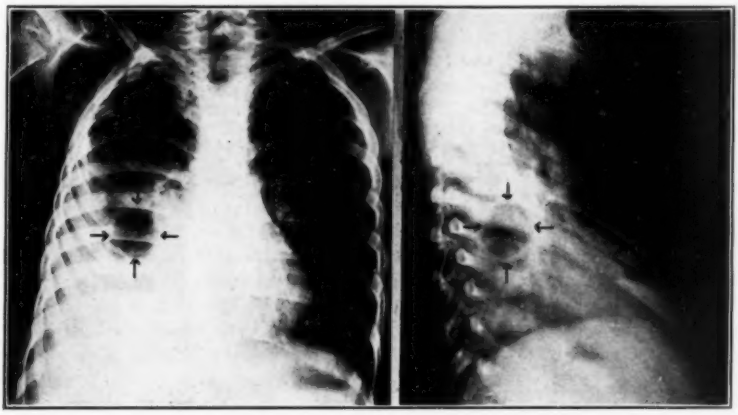

Fig. 6. Fig. 7.

Fig. 6.—Case 2, Jan. 6, 1934. There is a moderately large pleural exudate on the right side. An area of diminished density is visible in the right lower lung, close to the cardiac border.

Fig. 7.—Case 2, Jan. 6, 1934. Direct lateral view, showing the transparent area to be spherical and situated posteriorly in the right lower lobe. It is empty.

Roentgenologic Examination.—On Jan. 6, 1934, there was right-sided pleural exudate reaching a width of 3 cm. in the lower lateral portion of the chest. There was also infiltration in the lower portion of the right lung. In the lower lobe adjacent to the pleura there was an area of diminished density with a diameter of 2.8 cm. This was visualized not only in the ordinary posteroanterior film, but also in the right and left oblique and direct lateral films. This area did not contain any fluid (Figs. 6 and 7). On Jan. 10, 1934, films after bronchoscopy and lipiodol in-

stillation showed the chest to be essentially the same, except that the area of diminished density was considerably smaller and that none of the lipiodol had passed into it. On Jan. 17, 1934, it was very poorly demarcated, and by Jan. 26, 1934, it had disappeared. The pleurisy gradually resolved, and it had entirely disappeared by March 3, 1934. The area of diminished density did not reappear, and re-examination of the chest on April 7, 1937, showed it to be essentially normal. A small calcified area in the right axilla was present when he was first examined, and this probably accounted for the positive Mantoux test.

CASE 3.—M. S., female, 10 years old, was first seen in the Outpatient Department July 26, 1937. She was a well-developed, slightly undernourished pale girl with a temperature of 101.8° F. There were no abnormal physical findings in the chest. Mantoux test (1:1,000) was positive. No history of contact with tuberculosis could be established.

Roentgenologic Examination.—On July 28, 1937, the right root shadow was enlarged and contained calcification, and there was infiltration at the right base. Opposite the fifth rib anteriorly there was a circular area of diminished density about 2 cm. in diameter with comparatively thin, discrete margins. This did not contain any fluid. By Sept. 16, 1937, the area of diminished density had completely disappeared, and almost all the infiltration in the right lower lung had cleared. There was still calcification in and some enlargement of the right root shadow. On May 26, 1938, there was no evidence of recurrence of the area of diminished density.

CASE 4.—S. N., female, 9 years old, was admitted Nov. 23, 1937. She had become acutely ill five days previously with high fever and delirium followed by cough the next day and pain in the left side of the chest twenty-four hours before admission. She did not appear very ill, was fairly well developed, but somewhat undernourished and pale. Examination showed dullness in the left lower posterior part of the chest. She ran a remittent fever up to 102.4° F. for eight days after which the temperature remained normal. On Dec. 9, 1937, she was discharged.

Roentgenologic Examination.—On Nov. 23, 1937, there was pneumonia in the left lower lobe. By Nov. 30, 1937, the pneumonia had resolved considerably, but there was an oval area of decreased density in the lower portion of the left lung, opposite the fifth interspace anteriorly. This had a diameter of 2.4 cm. and contained a small quantity of fluid. It was still visible the next day, when oblique films showed it to be situated posteriorly in the lower lobe. There was a small overlying pleurisy. On Dec. 8, 1937, it was still very faintly visible but quite indistinct, and most of the infiltration in the lower portion of the left lung had disappeared. On Aug. 5, 1938, the chest was entirely clear.

CASE 5.—M. M., male, 2 years and 11 months old, was admitted March 15, 1933. Fever and cough had been present for five days. He was very ill, delirious, and had marked dyspnea with expiratory grunting and movement of the alae nasi. The nutrition was good. There were signs of consolidation in the left upper lobe. The fever subsided by lysis, the temperature reaching normal March 28, 1933. A slight cough persisted for another two weeks, but he was otherwise well and continued so throughout the remainder of his stay in the hospital, which lasted until May 22, 1933.

Roentgenologic Examination.—On March 16, 1933, there was an area of consolidation in the left lung extending from near the apex downward almost as far as the base. This cleared slowly so that considerable increased density still remained fifteen days later. On April 6, 1933, there was a suggestion of a rounded area of diminished density with a diameter of about 2 cm. in the left lung, opposite the second rib anteriorly. A small pleural exudate was present on the left side. The infiltration in the lung gradually diminished in extent, but the area of diminished density re-

mained, undergoing some slight fluctuation in size. By July 3, 1933, it was considerably more apparent, having a diameter of 3 cm. with thin and discrete margins. It did not contain any fluid. The final examination on Sept. 1, 1933, showed complete disappearance of the area of diminished density and clearing of the lung.

CASE 6.—J. J., male, 19 months old, was admitted Jan. 9, 1934. He had been coughing for five days, and fever, dyspnea, and expiratory grunting had been present for three days. He was a well-developed, well-nourished boy who did not appear very ill. There were dullness, diminished breath sounds, and moist râles over the right lower posterior part of the chest. His temperature became normal by Jan. 21, 1934, but after two days, it rose again because of bilateral otitis media. He was discharged well on Feb. 19, 1934.

Roentgenologic Examination.—On Jan. 10, 1934, there was consolidation involving the lower half of the right lung. Ten days later this had resolved slightly. There appeared to be a tiny "hole" surrounded by increased density in the right lung, situated opposite the seventh rib posteriorly. This transparent zone gradually increased in size, and by Feb. 1, 1934, the appearance suggested that two small "holes" were present. These were again shown on Feb. 8, 1934, situated opposite the third and fourth interspaces anteriorly. The larger had a diameter of 1.7 cm. and was surrounded by a thin, discrete margin. The smaller was just below and had a diameter of 0.9 cm. Laterally there was a small pleural exudate. By April 30, 1934, the "holes" had completely disappeared, and the chest was no longer abnormal excepting for a very tiny residual pleurisy.

CASE 7.—C. G., female, 10 months of age, was admitted Sept. 14, 1937. There was a history of pneumonia at six months of age, which cleared uneventfully. She had been coughing and had had fever for three days. Examination showed pneumonia at the right base. The temperature dropped gradually, reaching normal Sept. 19, 1937. She was discharged well Oct. 12, 1937, but was readmitted Nov. 21, 1937, with a third attack of pneumonia involving the left lower lobe. The fever subsided by crisis three days after admission, and she made the usual uneventful recovery. While in the hospital for gonococcal vaginitis, she developed pneumonia for the fourth time March 7, 1938. It was on the right side. The temperature gradually subsided over a period of five days, and she made a good recovery.

Roentgenologic Examination.—On Sept. 15, 1937, there was consolidation in the lower portion of the right lung. At that time the left base was quite clear. On Nov. 22, 1937, there was a pneumonia at the left base, and a circular area of diminished density, 8 mm. in diameter, was visible just lateral to the apex of the heart. By Nov. 30, 1937, the pneumonia of the left lower lobe had cleared, and the area of diminished density had disappeared. On Mar. 7, 1938, consolidation was demonstrated at the right base, the left base being clear.

CASE 8.—J. G., female, 2½ years old, was admitted Oct. 26, 1934. She had been coughing and had had fever for five days. She was a well-developed, well-nourished child, quite ill, with flushed cheeks, harsh cough, and expiratory grunting. There were dullness, bronchial breathing, and moist râles over the left upper lobe. The fever gradually subsided, and the temperature was normal by Oct. 30, 1934. She left the hospital well Nov. 27, 1934. She was readmitted on June 12, 1935, with pneumonia of the right upper and lower lobes, which resolved uneventfully, and she went home well June 29, 1935.

Roentgenologic Examination.—Examination Oct. 27, 1934, revealed an extensive left-sided pneumonia, extending from the apex almost to the base. By Nov. 9, 1934, this had undergone a good deal of clearing, but opposite the lower border of the third rib anteriorly on the left side, there was an area of diminished density measuring 1.3

cm. in width by 0.5 cm. in height. There was also a small pleural exudate in the lateral portion of the left side of the chest opposite the remaining consolidation. One week later there had been additional clearing of the pneumonia, and the area of diminished density was not definitely visible. On Dec. 10, 1934, the pneumonia had almost completely resolved, and there was no area of diminished density. Roentgenograms in June, 1935, showed a right-sided pneumonia which migrated from the upper to the lower portion of the chest and cleared in the course of sixteen days. The left lung remained normal in appearance throughout this illness.

CASE 9.—G. A., male, 19 months old, was admitted Sept. 17, 1935. There had been cough, fever, and grunting respirations for five days. He was a large, well-nourished, pale child with some dyspnea. On admission there were no definite signs of consolidation in the chest. He was given a transfusion of 200 c.c. of blood Sept. 22, 1935. His temperature dropped to normal abruptly Sept. 26, 1935, and he was sent home well Oct. 4, 1935.

Roentgenologic Examination.—On Sept. 18, 1935, there was pneumonia involving the upper portion of the left lung. This spread so that, by Sept. 26, 1935, it involved nearly all the left lung, particularly its lower part. By Oct. 3, 1935, most of the pneumonia had resolved, but there was a rounded area of diminished density in the left lung opposite the third interspace anteriorly. This area had a diameter of approximately 1.2 cm., and its margins were thin, rounded, and discrete. Contact with the patient was lost, so that no further examinations were possible.

CASE 10.—C. L., female, 11 months old, was admitted April 21, 1938. She had had an intermittent cough since her discharge from the hospital in November, 1937, when she suffered from an acute upper respiratory tract infection. Four days prior to the second admission, she developed a marked cough and refused some of her feedings; two days later, she began to have a high fever and became listless. She was fairly well developed, undernourished, and pale. The eardrums were reddened, and there was a purulent discharge from the right ear. The temperature ran an irregular febrile course due to complicating bilateral otitis media and mastoiditis. Bilateral mastoidectomy was performed May 27, 1938. She was discharged cured July 4, 1938.

Roentgenologic Examination.—On Nov. 3, 1937, there was nothing definitely abnormal except some increase of linear markings to the right base. On April 22, 1938, there was consolidation involving the right upper lobe. By May 2, 1938, the upper medial portion of the right upper lobe was clearing, but considerable consolidation still remained. Four days later there was still consolidation in the upper lobe, and, in addition to this, there was a circular area of diminished density with a diameter of 0.8 cm., situated opposite the first interspace and second rib anteriorly on the right side. On May 9, 1938, the consolidation had increased, but the area of diminished density was still visible in the same region. On May 13, 1938, the diminished density had disappeared and it did not reappear. The consolidation resolved gradually so that by June 6, 1938, most of it had cleared. A tiny pleural exudate appeared in the right upper chest after the disappearance of the area of diminished density, but this never became at all large.

CASE 11.—R. B., female, 2 years old, was admitted April 16, 1938. She had entered the hospital three times previously, in November, 1936, March, 1937, and January, 1938, with pneumonia which ran an uneventful course each time. She had had fever, cough, and occasional vomiting for three days and dyspnea, anorexia, and restlessness for 2 days. A mucopurulent discharge from the left ear was first noticed five days before admission. She was well developed and well nourished, acutely ill, very dyspneic, with rapid grunting respirations. She had an irregular fever up to

101.6° F. until May 22, 1938, with the exception of a period of ten days between April 20 and 30, 1938, when it remained normal. Postural drainage twice daily for one hour from May 24 to May 28, 1938, yielded no sputum whatsoever. She was discharged well on July 8, 1938.

Roentgenologic Examination.—On Nov. 3, 1936, bilateral bronchopneumonia was demonstrated. In March, 1937, there was pneumonia on the left side, and in January, 1938, pneumonia at the right base. On April 19, 1938, infiltration was present at both bases. By April 27, it had partially cleared. On May 4 there was a large area of consolidation in the left lung opposite the second, third, fourth, and fifth interspaces anteriorly. By May 13 consolidation involved nearly all the left lung, although its lower lateral portion was relatively clear. An area of diminished density was seen May 20, 1938, in the upper portion of the left lung, and a fluid level was visible within this area. The following day posteroanterior and right and left oblique films, as well as a film made with the patient lying on her right side, confirmed the presence of this area of diminished density and showed it to have a diameter of about 3 cm. It was more than half full of fluid and was surrounded by infiltration in the adjacent lung. On May 25, 1938, it was smaller and contained considerably less fluid, and the infiltration surrounding it was resolving. There was still an area of diminished density on May 31, 1938, and it was very faintly visible on June 10. It had disappeared by June 18, and by June 28, 1938, most of the infiltration had cleared. There was no evidence of recurrence.

CASE 12.—R. L., male, 8 months old, was admitted April 26, 1934. He had been well until five weeks previously when he began to cough; the coughing was followed occasionally by yellowish sputum. There had been fever for nine days and dyspnea, expiratory grunting, and anorexia for four days before admission. He was well developed, somewhat undernourished, slightly cyanosed, and breathing rapidly. There were slight dullness, diminished breath sounds, and moist râles over the right base posteriorly. He developed bilateral otitis media and chicken pox. On May 23, 1934, he showed signs of pneumonia involving the right upper lobe, and the temperature rose to 104° F. This persisted until May 30, with a few temperature rises to 102.9° F. after that. Postural drainage daily for three weeks yielded no sputum, and it was discontinued June 16. He was sent home in good condition June 29, 1934, although there was still some discharge from both ears.

Roentgenologic Examination.—On April 27, 1934, there was a rather extensive consolidation involving most of the right lung except its upper portion. By May 11 a large portion of it had disappeared. On May 25 there was dense consolidation in the right upper lobe, as well as some infiltration in the lower medial portion of the right lung. On June 5, 1934, a large area of diminished density, 2 cm. in width and 3 cm. in height, had appeared in the right upper lobe, opposite the first and second interspaces anteriorly. This was surrounded by infiltration. By June 11 it had almost disappeared, but infiltration still remained, particularly in the lung above it. On June 20 there was still residual infiltration in the right upper lung but no definite area of diminished density. Re-examination on Jan. 5, 1939, revealed no abnormality of either lung.

CASE 13.—P. D., male, 2 years old, was admitted May 17, 1938. He had been coughing for ten days with fever up to 105° F. for eight days and had some epigastric pain. He was fairly well developed and nourished, acutely ill, with flushed face, dyspnea, and hacking cough. The breath sounds were impaired over the left upper lobe. By May 20, there was acute right purulent otitis media, necessitating myringotomy. On May 22, he was given a blood transfusion of 200 c.c. The temperature, which was high with slight remissions, dropped to normal abruptly on May 28. It rose slightly on two occasions during the following week, and there

was intermittent fever up to 102.4° F. during the next week. Thereafter the temperature remained normal. On June 7, 1938, there was a slight cough but no sputum. On June 21 the chest had partially cleared, and the boy was discharged, feeling well.

Roentgenologic Examination.—On admission there was consolidation in the left upper lung, extending downward as far as the third rib anteriorly. Four days later this consolidation had spread so that it also involved the lower portion of the left side of the chest. On June 3, 1938, posteroanterior, oblique, and direct lateral upright films, as well as a posteroanterior film with the patient lying on his right side, revealed the consolidation to be entirely in the upper lobe of the left lung, the lower lobe being clear. A cluster of four areas of diminished density was demonstrated in the upper portion of the left upper lobe. None of these extended downward beyond the second rib anteriorly. They contained a moderate amount of fluid. They were still present June 7, 1938, but not so apparent. Three days later, an area of diminished density, somewhat irregular in shape and containing a small amount of fluid, was visible opposite the first rib and first interspace anteriorly. Consolidation remained surrounding this area, but the lower portion of the chest had almost cleared. On June 16, 1938, there was still a trace of this transparent area in the upper portion of the left lung. By July 4, 1938, there was a small amount of residual infiltration at the left apex, but no diminished density was visible.

CASE 14.—R. B., male, 5 years old, was admitted June 6, 1938. He developed measles April 26, 1938, and was allowed up nine days later. Cough, sore throat, headache, general malaise, sneezing, and a chill appeared on that day, and he continued to be ill thereafter and consequently was sent to the Alexandra Hospital May 16, 1938. The temperature on admission there was 105° F.; the pulse rate, 140 per minute; and the respiratory rate, 30 per minute. He looked quite ill. His throat was slightly reddened, and the right base of the chest presented dullness, faint breath sounds, and moist râles. Ten cubic centimeters of clear straw-colored fluid were aspirated from this region; from the fluid were isolated pneumococci which did not belong to Types I-VIII. The boy's general condition improved and the fever gradually subsided, but the signs at the right base persisted. On May 31 the temperature rose to 101.6° F. and remained above normal with daily remissions for five days. The respiratory rate was 30. On June 6 aspiration yielded no fluid. He was then transferred to the Children's Memorial Hospital. He was pale and thin, weighing 39 pounds, but not acutely ill. There was a loose cough. The chest signs at the right base remained as previously noted, and on June 14 thoracentesis was again performed, but no fluid was obtained. He improved after that and was discharged July 29, 1938.

Roentgenologic Examination.—On June 7, 1938, posteroanterior and oblique films demonstrated a moderately large pleural exudate on the right side, situated mainly in the posteroinferior portion of the right pleural cavity. There was also some infiltration in the lower portion of the right lower lobe. On June 13, 1938, there was very little change. On June 18 a rounded area of diminished density was visible in the right side of the chest, just lateral to the right root shadow. This was 1.5 cm. in width and 2 cm. in height. It contained little, if any, fluid. Oblique examination showed it to be situated well posteriorly in the chest. Ten days later it had disappeared, and the increased density in the lower portion of the right side of the chest had cleared considerably. On July 8, 1938, there was still a tiny residual pleural exudate on the right side, but no area of diminished density was visible.

CASE 15.—N. R., male, 7 years old, was admitted May 10, 1938. He had typhoid fever and developed pneumonia during convalescence toward the end of July, 1938. He made an uneventful recovery.

Roentgenologic Examination.—On May 11, 1938, there was some slight general increase of linear markings throughout both lungs. On July 26, 1938, a large fan-shaped area of infiltration was visible extending outward and upward from the region of the right root shadow. Opposite the second interspace and third rib anteriorly on the right side there was an area of diminished density, 2.5 cm. in diameter. This had a rather smooth, discrete margin and did not contain any fluid. The interlobar fissure between the right upper and middle lobes was superimposed on it. By Aug. 24, 1938, practically all the infiltration had disappeared, but there was a very thin-walled area of diminished density lateral to the root shadow with a diameter of 3.2 cm. It was again quite empty. This area was again demonstrated on Sept. 19, 1938, and at the last examination, on May 8, 1939.

CASE 16.—E. A., male, 13 years old, was admitted Feb. 20, 1936. He had been ill with fever, headache, chills, and pain in the back for four days. He was a well-developed, well-nourished boy, quite toxic, with flushed cheeks. There was evidence of consolidation in the right side of the chest and a friction rub at the right base. He developed signs of fluid, and on Feb. 24, 1936, right thoracentesis yielded 75 c.c. of sanguinopurulent fluid from which a culture of *Staphylococcus pyogenes* was grown. On Feb. 27, 1936, 400 c.c. were aspirated from the right hemithorax. Closed drainage was instituted Feb. 28, 1936, and thoracotomy with insertion of a drainage tube was performed March 5, 1936. The tube was removed April 4, 1936, and the boy was discharged well April 23, 1936.

Roentgenologic Examination.—On Feb. 21, 1936, there was infiltration at the right base as well as a moderate-sized area of pleurisy. There was also a rounded area of decreased density, 3 cm. in diameter, situated well posteriorly in the right lower lobe, opposite the ninth posterior rib and ninth posterior interspace. This contained a very small amount of fluid and was demonstrated in posteroanterior, direct lateral, and in right and left oblique films. It was also shown in a posteroanterior film taken with the patient lying on his left side. Three days later, a large amount of fluid had formed in the right pleural cavity, but the area of diminished density could still be faintly seen. Pleural fluid was aspirated but re-formed rapidly, and drainage was instituted. The area of diminished density was seen in subsequent examinations through the fluid, and it remained empty. It was displaced medially when fluid accumulated in the pleural cavity. By March 9, 1936, it had attained a diameter of 3.5 cm. and was quite rounded with a thin, discrete margin. It was still present March 20, but very much smaller and empty; by April 9 it had disappeared. On May 26, 1936, the lung was well re-expanded. There was no sign of any recurrence of the area of diminished density in subsequent examinations of the chest.

CASE 17.—R. V., female, 8 years old, was admitted Dec. 7, 1937. She had become acutely ill two weeks previously with fever, cough, and some vomiting, and pneumonia was diagnosed. After a week the fever subsided but rose again and was accompanied by pain in the chest, and there was malaise three days before admission. She was a thin, pale girl with marked dyspnea and appeared very toxic. There were signs of a large amount of fluid in the right hemithorax. Between Dec. 17, 1937, and Jan. 3, 1938, 1400 c.c. of fluid were removed from the right pleural cavity. Culture yielded Type VIII pneumococci. On Jan. 4, 1938, closed drainage with two rubber tubes was established, and this proved adequate. On Feb. 16, 1938, the temperature, which had been more or less above normal since admission, rose to 102° F. and ran along up to 105° F. until Feb. 24, 1938. This was due to pneumonia of the left lower lobe which resolved satisfactorily. Her course was rather stormy during January and February, and she became quite emaciated but began to show definite improvement about the middle of March. There was no discharge from the wound after April 15, 1938.

Roentgenologic Examination.—On admission there was a large collection of fluid in the right pleural cavity. This was drained, but the right lung did not expand satisfactorily. On Jan. 10, 1938, there was no fluid in the right pleural cavity, but an area of diminished density was present in the partially collapsed right lung, opposite the second interspace anteriorly, close to the vertebral column. This persisted and soon became larger. It was shown in several examinations, and by Jan. 25, 1938, it contained a small amount of fluid. It then had a diameter of 3.5 cm., and there was also a smaller central area of diminished density about 1 cm. in diameter, superimposed on the larger area. In the next six days they increased in size and then almost disappeared, only to reappear on Feb. 17, 1938. At this date, they were empty and had thin discrete margins. The last time there was any trace of these areas of diminished density was March 18, 1938. Examinations since then have shown no recurrence.

CASE 18.—T. L., female, 1 year old, was first examined Dec. 15, 1932. She had been perfectly healthy up to the age of 9 months, when she weighed 27 pounds. She then became ill, and a physician who attended her for ten days diagnosed the condition as pneumonia. She had some cough and "noisy breathing" from time to time and had lost weight. During the preceding two weeks there had been more marked dyspnea and night sweats. She was a well-developed, poorly nourished (weight, 15 pounds and 14 oz.), pale girl with moderate dyspnea and slight cyanosis.

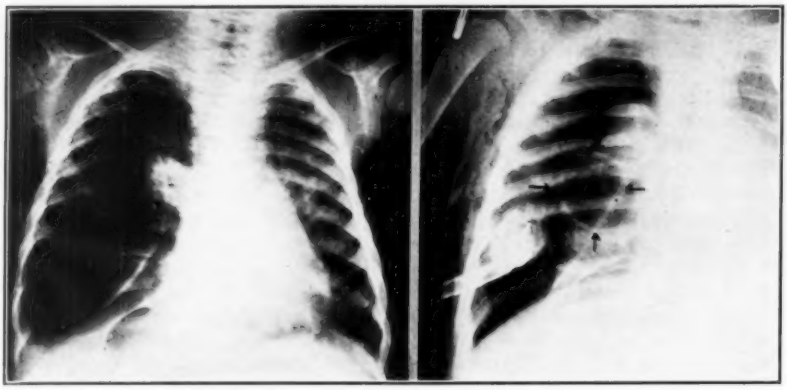

Fig. 8. Fig. 9.

Fig. 8.—Case 18, Dec. 15, 1932. There is a large right-sided pneumothorax. The area of diminished density is scarcely visible in the illustration, although it was shown plainly in the original roentgenogram.

Fig. 9.—Case 18, Dec. 29, 1932. The positive pressure in the right pleural cavity has been relieved by the insertion of a needle, and the right lung is not as completely collapsed as formerly. The area of diminished density is now distinctly visible in the central portion of the chest.

The breath sounds were diminished on the right side, and the heart was displaced to the left. By Dec. 28, 1932, the dyspnea and cyanosis were more marked. During an attempted manometric reading from the right side of the chest, the fluid in the manometer was forced out in a jet 3 feet high. About 200 c.c. of air was withdrawn by syringe. She was temporarily somewhat relieved by allowing the air to escape intermittently under water through a clamped tube. As she was getting worse, a thoracotomy was done Jan. 5, 1933, but the lung was not as well exposed as was planned, owing to the child's poor condition. A ruptured ballooned area was found; and an attempt was made to close the opening in the pleura by a purse-string suture, but air emerged through the needle holes. The temperature

ranged up to 103° F. until Jan. 8, 1933, but subsequently it remained normal. She was definitely improving by Jan. 14, 1933, and on Jan. 31, she was discharged in good condition. She continued well until she was readmitted July 5, 1933, with bronchopneumonia. She had a remittent fever up to 105° F. for ten days and made a good recovery.

Roentgenologic Examination.—On Dec. 15, 1932, the heart and trachea were displaced to the left. There was an extremely large right-sided pneumothorax associated with marked collapse and compression of the right lung. In the central portion of the chest, an oval area of diminished density was visible with its longest diameter lying obliquely and measuring 4 cm. (Fig. 8). This was persistently present in many examinations (Fig. 9). A film made shortly after thoracotomy showed the area of diminished density a little smaller than before, but still present. By Jan. 25, 1933, there was evidence of some re-expansion of the right lung and considerably less cardiac displacement, but the area of diminished density was still visible. On May 5, 1933, the right lung had completely re-expanded and there was no longer any area of diminished density in the right side of the chest (Fig. 10). A rather large pneumonic area was shown on the left side on July 6, 1933, but no

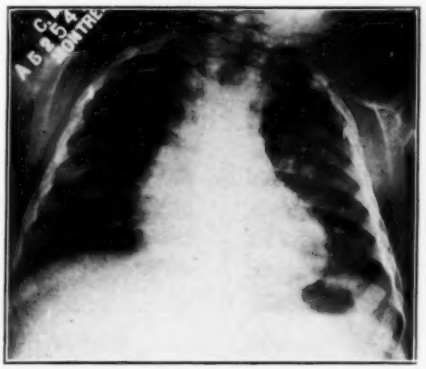

Fig. 10.—Case 18, May 5, 1933. The pneumothorax has disappeared, and there is no longer any demonstrable abnormality of the right lung.

abnormality could be seen in the right lung. On Aug. 16, 1933, the left side of the chest had almost cleared. At no time did any fluid develop in the right pleural cavity despite the large pneumothorax, except for a very small amount following thoracotomy.

Case 19.—E. L., male, 2 months old, was admitted June 8, 1936. He had failed to gain weight since birth, and diarrhea had been present for three days prior to admission. He was very poorly nourished (6 pounds, 13 ounces). There were no other physical findings. On proper feedings he gained weight for a few weeks, then began to cough, and on July 16, 1936, rapidly became dyspneic, dehydrated, and cyanosed. There were a few moist râles in the right side of the chest. The following morning there were dullness and diminished breath sounds over the left upper lobe, and fine moist râles were scattered throughout the chest. The temperature was normal except for three occasions, when it rose to between 100° and 101° F., and just before death on July 17, 1936, it reached 101.6° F. Necropsy revealed chronic bilateral interstitial and lipoid pneumonia, interstitial emphysema of the left lung with intrapleural bullae, rupture of an intrapleural bulla with massive atelectasis of the left lung, mild colitis, and mild periportal hepatitis.

Roentgenologic Examination.—On July 17, 1936, the heart and mediastinum were displaced to the right. There was a large left-sided pneumothorax with about 85 per cent collapse of the left lung. The right lung presented considerable hazy increased density. The only portions which were relatively clear were the extreme apex and its lower lateral portion. No definite areas of diminished density were demonstrated in either lung.

CASE 20.—C. D., male, 6 months old, was admitted Sept. 15, 1934. He was a full-term infant, weighing 7 pounds and 8 ounces at birth. There had been a purulent discharge from the right ear for six weeks. He had begun to run fever Aug. 28, 1934. Diarrhea commenced five days later and cough the next day. The breath sounds over the left side of the chest were diminished. On Oct. 29, 1934, distant bronchial breathing and moist râles were heard over the left hemithorax. The infant died Nov. 5, 1934. Necropsy showed a congenital cyst of the upper lobe of the left lung, probably bronchial in origin, chronic peribronchitis of the left lung, and mild acute peribronchitis of the right lung.

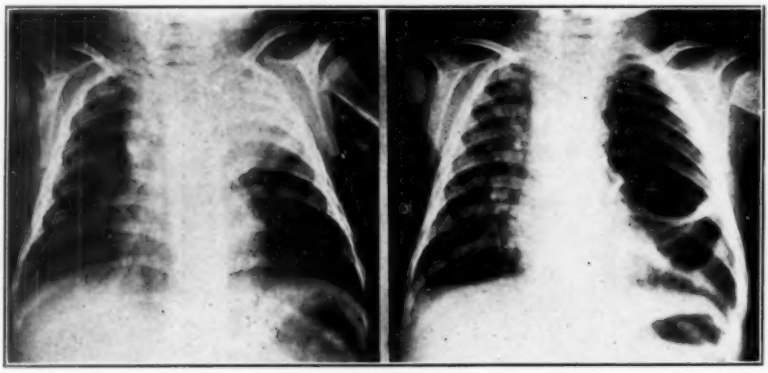

Fig. 11. Fig. 12.

Fig. 11.—Case 20, Sept. 4, 1934. A large area of increased density is present in the upper portion of the left lung. There is displacement of the heart and trachea to the right.

Fig. 12.—Case 20, Oct. 24, 1934. An area of diminished density occupies almost all the left side of the chest. Autopsy revealed a congenital cyst of the left upper lobe.

Roentgenologic Examination.—On Sept. 4, 1934, there was a large area of increased density in the upper portion of the left lung. The heart and trachea were slightly displaced to the right (Fig. 11). Nine days later very little change had occurred. On Sept. 17, 1934, an area of diminished density with a diameter of 1.5 cm. had appeared in the left upper lung. This was surrounded by increased density which also extended downward and obscured the left border of the heart. The area of diminished density persisted, gradually increased in size, and remained empty. By Oct. 24, 1934, it occupied nearly all the left side of the chest. At this time there was practically no cardiac displacement (Fig. 12).

CASE 21.—T. W., male, Chinese, 2 months old, was admitted on Sept. 4, 1934. He had been coughing, refusing feedings, losing weight, and vomiting occasionally for three weeks. His condition was poor, and he was very emaciated and weighed 6 pounds. He had a frequent harsh cough. The respirations were 40 per minute. There were lagging of the right side of the chest, dullness and impaired breath sounds over the right upper part anteriorly and posteriorly, and coarse and sibilant râles were heard at the right base posteriorly and in the axilla. A soft, systolic

apical murmur of the heart was present. On Sept. 6, 1934, he became cyanotic while taking his feeding and died soon after. A large tuberculous cavity, measuring 4 cm. in diameter, occupying the posterior two-thirds of the upper lobe of the right lung, was found at autopsy. It contained air and pus and was connected with a small bronchus. Smears from the wall showed tubercle bacilli. There were bilateral tuberculous bronchopneumonia, miliary tuberculosis, tuberculous pericarditis, pleural adhesions in the right pleural cavity, and a small left pleural effusion.

Roentgenologic Examination.—On Sept. 5, 1934, there was a cavity in the upper portion of the right side of the chest, measuring 4.5 cm. in height, 3 cm. in width, and 4.5 cm. anteroposteriorly. This contained considerable fluid and was surrounded by dense lung tissue. It did not have a thin, fine margin. There was also depression of the great fissure on the right side. The trachea was very fractionally displaced to the left, but there was no cardiac displacement. There was mottling throughout the remainder of the lungs (Figs. 13 and 14).

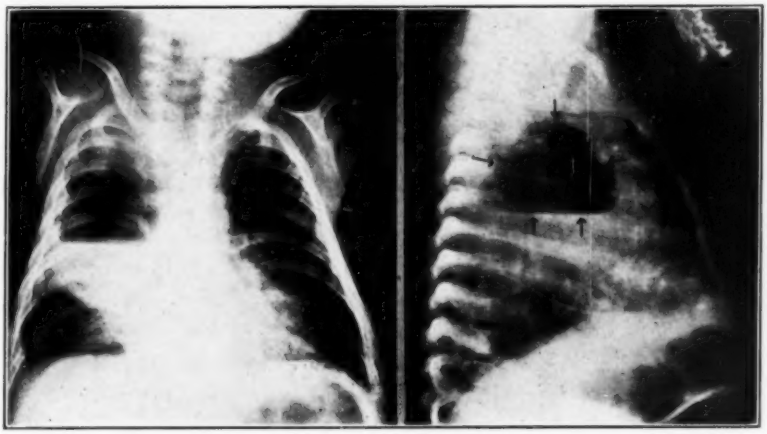

Fig. 13. Fig. 14.

Fig. 13.—Case 21, Sept. 5, 1934. There is a very large cavity of the right lung, and this contains considerable fluid. There is also mottling throughout the remainder of the right lung and the left lung.

Fig. 14.—Case 21, Sept. 5, 1934. Lateral view showing anteroposterior extent of the cavity and the depression of the great fissure of the right side. Autopsy showed a very large tuberculous cavity in the upper lobe of the right lung.

Cases 1 to 15 inclusive represent typical uncomplicated instances of localized bullous emphysema associated with pneumonia. In general, these children did not cough any more nor were they sicker than the ordinary run of children with pneumonia. Cases 16 and 17 show the condition complicated by empyema. In Cases 18 and 19 pneumothorax developed as a result of rupture of the pleura over the bullous emphysematous spaces.

The ages of the children ranged from 3 months to 13 years. There were ten boys and nine girls. None of the children showed any clubbing of the fingers, and none had any foul sputum. Usually there were no signs or symptoms ascribable to the bullous emphysema, and the

temperature, pulse, respiration, and leucocyte count remained normal, unless some complication was present. The condition was recognized from the appearance of the roentgenogram. Case 20 is included to show a congenital air cyst of the lung, proved at necropsy, in contrast to bullous emphysema; and Case 21, to illustrate a proved tuberculous cavity in the lung.

DIFFERENTIAL DIAGNOSIS

The characteristic picture is present when the surrounding lung field is comparatively clear; but when there is infiltration around the emphysematous space, the decreased density is less marked and the contour is not as sharply defined, making it very difficult, or sometimes impossible, to rule out lung abscess. However, a more typical appearance results as the lung clears, and this is coincidental with clinical improvement and absence of purulent sputum. It may take a week or so to differentiate definitely between bullous emphysema and lung abscess, especially when fever and leucocytosis persist, because of some infection such as otitis media, etc. It is neither advisable nor necessary in the majority of such children who are recovering from recent pneumonia to inject lipiodol or perform diagnostic pneumothorax. These emphysematous spaces can readily be shown to be actually within the lung, and there is no evidence of any pulmonary collapse such as would be present with a localized pneumothorax. In true congenital air cyst, the wall is usually thicker and not so smooth, and one would not expect such complete rapid resolution. Occasionally, it may be advisable to exclude diaphragmatic hernia by examination of the gastrointestinal tract with barium.

DISCUSSION

From a clinical point of view one need hardly maintain a distinction between emphysematous bullae and blebs; in fact, the terms have often been interchanged. The distended air space may actually consist of more than one bulla with ruptured or unruptured septa between them. It would seem appropriate to group bullae and blebs together and refer to them as localized bullous emphysema. It is unwise to use the term "cyst" or "cystic" in referring to this condition, as this leads to confusion with true congenital pulmonary air cyst.

The more frequent roentgenologic examinations of the chests of children with pneumonia which have been made in recent years, as well as the improved technique, probably account for the comparatively common finding of this condition. It is interesting and possibly significant to note that no such instance has been found in a large number of children with primary pulmonary tuberculosis nor in many with more advanced pulmonary tuberculous lesions who have been examined roentgenologically repeatedly during the same number of years.

Only two of the children in our series had positive tuberculin tests. Both of them were obviously suffering from pneumonia which resolved in the usual manner and showed no evidence of pulmonary tuberculosis. All of the children had negative Wassermann tests.

Nothing to suggest localized bullous emphysema has been encountered in roentgenograms of the chests of healthy children.

The most likely pitfall in the interpretation of the roentgenographic picture in bullous emphysema is to mistake it for lung abscess. Indeed, some cases so diagnosed which have not exhibited the usual clinical features and which terminated in what has been considered a "spontaneous cure," have doubtless represented instances of this condition. It would also seem that many instances of so-called congenital solitary lung air cyst have been cases of localized bullous emphysema. Thus, the report of Crosswell and King[20] of an infant who had a balloonlike inflated space in the left lung which disappeared following injection of lipiodol and repeated aspirations of air, resembles one of our cases (Case 18) in many respects. Schenck[21] has included in his collection of 160 cases of congenital cystic disease of the lungs some which may well be localized bullous emphysema. Whereas this condition is fairly commonly associated with pneumonia in children, true congenital lung cyst is comparatively a very rare finding. Lederer[22] found none in 5,000 consecutive autopsies. At the Children's Memorial Hospital in Montreal, one (Case 20) has been observed in 903 autopsies in the last 9 years. We feel that the roentgenographic appearance which has been ascribed to so-called "aputrid pulmonary necrosis" of the lung may really be that of localized bullous emphysema.

The most probable explanation of the formation of localized bullous emphysema associated with pneumonia would seem to be plugging of a bronchiole with mucus or exudate, producing an obstruction of ball-valve type. Air enters the surrounding lobule more readily than it can emerge from it. This results in its dilatation, and kinking of the bronchiole may help to accentuate the obstruction. Rupture of the alveolar walls may occur, forming a large air pocket. Air may track subpleurally or intrapleurally, forming a voluminous balloonlike emphysematous space. If the pressure rises sufficiently the pleura may rupture, giving rise to pneumothorax, as occurred in Cases 18 and 19. Under these conditions even alarming symptoms of increasing intrathoracic tension, such as cough, dyspnea, and cyanosis may develop, as in Case 18, necessitating aspiration of air or surgical intervention. Ordinarily, however, localized bullous emphysema requires no treatment. One can only conjecture as to what happens when such emphysema disappears. Rupture into a contiguous lobule may occur, so that the air escapes through a communicating patent bronchiole; or the ball-valve obstruction may be removed suddenly; or it may

become gradually less and less. In the former instances the emphysematous space disappears abruptly; while in the latter, which is probably what usually takes place, it tends to slowly reduce in size and eventually disappear.

SUMMARY

Attention has been drawn to the condition of localized bullous emphysema associated with pneumonia, which has been practically overlooked, even in the more recently published pediatric textbooks. This is certainly common enough to warrant a complete description in all volumes dealing with the diagnosis of diseases of the lung in infants and children.

The term "cyst" or "cystic" should not be applied to this condition. In contrast, true congenital pulmonary air cyst is encountered very rarely. It should be emphasized that all our cases have been associated with pneumonia and frequently with some degree of pleurisy, often quite localized in the affected region. There may be an accompanying empyema or, if rupture of the pleura occurs, pneumothorax. We have not encountered it in children with pulmonary tuberculosis without pneumonia; nor have we observed any such instance in roentgenograms of normal children's chests.

The characteristic roentgenologic appearance of localized bullous emphysema consists of one or more abnormal areas of diminished density, surrounded by thin, dense, smooth margins. These are spheroid or ovoid in shape, and sometimes loculated. They are easily seen when the surrounding lung is comparatively clear; on the other hand, they may be merely suspected at first when infiltration is present in the contiguous lung, but they become more definite as this clears in subsequent examinations. Their location is usually subpleural or intrapleural. They may contain some fluid, but as a rule only a small amount. The size varies from very small, when they may be hardly distinguishable, to voluminous balloonlike spaces, which may occupy a large portion of one lung. Variations in size occur from time to time until they eventually disappear. Usually this takes place in a few weeks, but occasionally some months may elapse before the chest returns to normal.

This condition is not accompanied by any abnormal signs or symptoms, unless enormous inflation results or the pleura ruptures with the formation of pneumothorax, giving rise to evidence of increased intrathoracic pressure.

The differential diagnosis between bullous emphysema and lung abscess, localized pneumothorax, congenital pulmonary air cyst, and diaphragmatic hernia is not difficult, if the course of the case can be followed for a short time.

No treatment is necessary unless complicating conditions ensue.

REFERENCES

1. Fishberg, M.: Arch. Int. Med. **20**: 739, 1917.
2. Sampson, H. L., Heise, F. H., and Brown, L.: Am. Rev. Tuberc. **2**: 664, 1919.
3. Amberson, J. B.: Am. J. Roentgenol. **12**: 438, 1924.
4. Sergent, E.: Presse méd. **47**: 509, 1924.
5. Miller, W. S.: Am. J. Roentgenol. **15**: 399, 1926.
6. Laurell, H.: Acta. radiol. **10**: 72, 1929.
7. Hayashi, J.: Frankfurt. Ztschr. f. Path. **16**: 1, 1914.
8. Fischer-Wasels, B.: München. med. Wchnschr. **74**: 1877, 1927.
9. Kjaergaard, H.: Acta. med. Scandinav. Sup. No. 43, 1932.
10. Jäderholm, K. B.: Acta. radiol. **13**: 51, 1932.
11. Miller, W. S.: Am. Rev. Tuberc. **28**: 359, 1933.
12. Freedman, E.: Am. J. Roentgenol. **35**: 324, 1936.
13. Duken, J.: Ztschr. f. Kinderh. **43**: 339, 1927.
14. Vollmer, H.: Ztschr. f. Kinderh. **46**: 810, 1928.
15. Kleinschmidt, H.: Monatschr. f. Kinderh. **46**: 205, 1930.
16. Zarfl, M.: Ztschr. f. Kinderh. **54**: 92, 1933.
17. Peirce, C. B., and Dirkse, P. R.: Radiology **28**: 651, 1937.
18. Lereboullet, P., Lelong, M., and Bernard, J.: Bull. Soc. pédiat. de Paris **34**: 77, 1936.
19. Kessel, L.: Arch. Int. Med. **45**: 401, 1930.
20. Crosswell, C. V., and King, J. C.: J. A. M. A. **101**: 832, 1933.
21. Schenck, S. G.: Am. J. Roentgenol. **35**: 604, 1936.
22. Lederer: Personal communication to Schenck.[21]

AN ORIGINAL METHOD OF OBTAINING SPUTUM FROM INFANTS AND CHILDREN

With Reference to the Incidence of Pneumococci in the Nasopharynx

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THE method of obtaining sputum from infants and children by the use of the so-called laryngeal swab is quite unsatisfactory. It is often necessary to obtain more than one specimen before one is sure of the predominating organism and sufficient sputum for a direct smear examination is uncommon. The preliminary broth incubation is also time consuming. The other recognized method of obtaining sputum is by the use of the stomach tube, which is best suited for examination for tubercle bacilli. Faced with these problems in the diagnosis and treatment of pneumonia in children, a new suction method of obtaining sputum was devised and has been used for the past two years. It has entirely replaced the former methods of obtaining sputum from infants and children in this hospital.

The suction method can be used to obtain sputum from either the larynx or nasopharynx. We have found that sputum from the nasopharynx is best suited to typing pneumococci. In cases of pneumonia due to mixed infection, tuberculosis, or whooping cough the laryngeal route is most reliable.

LARYNGEAL METHOD

This method consists of aspirating sputum from the throat while the child coughs.

The apparatus consists of an ordinary glass 50 c.c. syringe, a 2-inch piece of soft rubber tubing of 3/16 inch inside diameter with a small hole cut in one side (so that the thumb can easily cover the hole and thus act as a valve), a 2-inch piece of glass tubing of ¼ inch outside diameter, and a 3- to 4-inch piece of slightly curved stiff rubber tubing or catheter of ⅛ inch inside diameter with a notch cut in either side of the tip. The piece of soft rubber tubing is slipped over the tip of the syringe and is connected to the catheter with the short glass tube. When assembled, it consists then of a catheter to enter the child's throat, a glass tube connection for the observation of the sputum, a valve to permit alternate suction and escape of air from the syringe,

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and an ordinary 50 c.c. syringe to provide the suction. The apparatus when boiled is ready for use. All these materials are to be found in any hospital storeroom.

The assistance of one nurse is required. She stands at the head of the bed holding the arms of the child firmly above his head. The operator stands at the patient's right. The barrel of the syringe is held with the left hand, with the thumb covering the hole of the valve. The right hand first holds the end of the catheter which is quickly inserted towards the uvula until the child gags or coughs and opens his mouth widely. The right hand then changes position grasping the handle of the piston and suction is commenced with the tip of the catheter as close to the larynx as possible. Suction is performed by pulling the piston out with the right hand with the left thumb at the same time covering the hole in the soft rubber tube or valve. At the end of the up-stroke the thumb

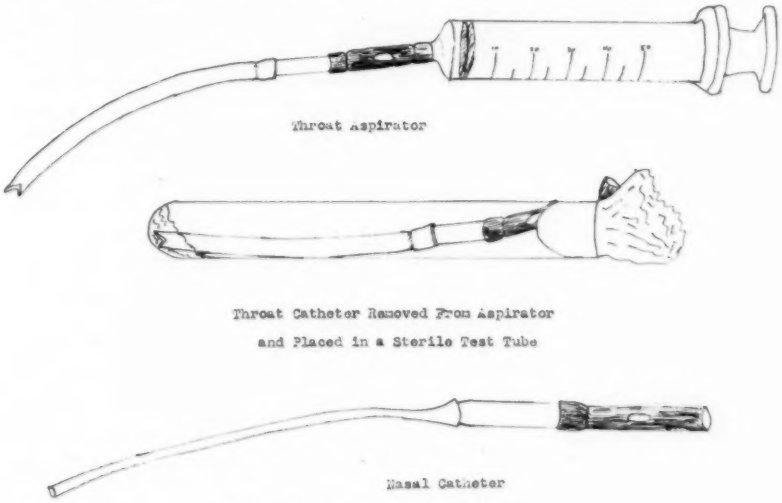

Fig. 1.—Diagrams of apparatus.

is removed from the hole, and the piston is shoved back into the barrel. In this manner the sputum is not returned into the throat by the in-stroke of the plunger, and by fast, repeated in- and out-strokes of the plunger, coordinated with the removal of the thumb on every in-stroke, a powerful intermittent suction is obtained. This strong suction in the back of the throat serves to aspirate sputum from the larynx and also to irritate the cough reflex thus making the cough more explosive. In older children it is best first to encourage them to cough and expectorate into a sputum cup, and, when the cough sounds loose or if they do not seem successful with their own efforts, then to use the suction method. It might be added that once the catheter is at the back of the throat and the child is coughing it is unusual for the child to seize the catheter

with his teeth. The whole procedure should be done quickly and energetically since the child is unable to breathe properly during the operation.

When the sputum is seen to rise into the glass tubing, the catheter is removed from the mouth and placed in a sterile culture tube. Then the sputum is forcibly driven out of the catheter by the syringe into the tube. One should be careful to grasp firmly the proximal inch of the piston with the forefinger and thumb of the right hand, otherwise the piston may be driven through the end of the barrel. Having transferred the sputum to the culture tube, the valve is then removed from the syringe and the catheter and valve are left in the culture tube, which is then corked and labeled and is ready for the laboratory examination.

In the laboratory, saline is added to the sputum in the culture tube. Also saline may be drawn up into the catheter to obtain additional sputum from the catheter if necessary. The culture tube is then emptied into a Petri dish for the examination of the sputum. The valve and catheter are cleaned with fast running water. The whole apparatus is reassembled, sterilized by boiling, and wrapped in a sterile towel. It is then again ready for use. Several sterile outfits should be kept available.

The sputum is best obtained about one to two hours after a meal, otherwise vomiting may result. This method requires considerable practice and perseverance to obtain best results, but after some experience there should be little difficulty in obtaining sufficient sputum for examination. Occasionally one is unable to obtain anything by suction, but the irritation itself may cause the child to cough and expectorate.

The method is suitable for obtaining sputum for examination for tubercle bacilli in children. Its use also is indicated in cases of suspected whooping cough since the sputum may be examined by direct smear and suitable particles spread over proper media instead of using the cough plate method.

Finally the operator is advised to wear a mask.

Replacing the rubber tube with the side hole by some type of mechanical valve has been considered, but this would complicate the process of cleansing the apparatus. The outfit as used is the essence of simplicity.

NASOPHARYNGEAL METHOD

This method again employs the principle of suction to obtain sputum but requires a slightly different equipment. The stiff rubber throat catheter is replaced by a 7-inch rubber tube, the diameter of which depends on the child's nares, but in general a No. 9 French catheter is suited to infants up to the age of 6 months, and a No. 10 is satisfactory for children over this age. The nasal catheter is passed through the nares until it is judged to have reached the adenoid area. Suction

is then commenced, and is continued while the catheter is slowly withdrawn from the nose. The child does not need to cough.

Fig. 2.

Fig. 4.

Fig. 2.—Photomicrograph of direct smear of sputum from nasopharynx showing Type XIX pneumococci. (×1350 diameters, Gram's stain.)

Fig. 3.—Photomicrograph of direct smear of sputum from larynx showing mouth organisms as well as Type I pneumococci. (×1350 diameters, Gram's stain.)

Fig. 4.—Photomicrograph of direct smear of sputum from nasopharynx showing colony formation of Type I pneumococci. (×1880 diameters, Gram's stain.)

In our experience this method of obtaining sputum has been found ideal for typing pneumococci. Sputum from this source can always be obtained and is always free from mouth organisms. A minimum of experience is required by the operator. In our cases of early severe pneumococcic pneumonia the pathogenic type has been found by the

direct Neufeld examination in about 90 per cent of the cases and in about 100 per cent of cases after a mouse passage. (During the past winter 400 cases of pneumonia have been typed at this hospital.) The only criticism offered is the frequency with which multiple types are encountered (usually two but occasionally three). In about 12 per cent of the cases two types of pneumococci were recognized by direct typing. In another 12 per cent of the cases a second type was recognized after passage through a mouse. When pneumococci are not seen in the sputum from the nasopharynx in a case of pneumonia, the sputum from the larynx will probably reveal that the causative organism is one other than the pneumococcus.

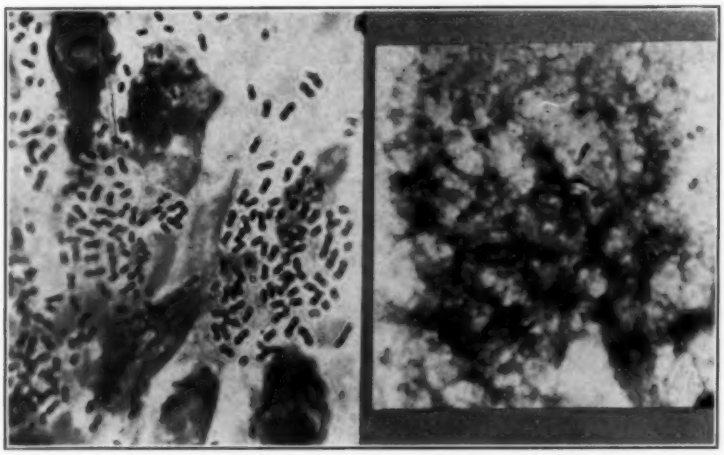

Fig. 5. Fig. 6.

Fig. 5.—Photomicrograph of direct smear of sputum from nasopharynx of child with early pneumonia showing Type II pneumococci. (×1350 diameters, Gram's stain.)

Fig. 6.—Photomicrograph of direct smear of sputum from larynx of a 6-month-old infant with pulmonary tuberculosis showing tubercle bacilli. (×1880 diameters, acid-fast stain.)

We have found the nasopharyngeal method of sputum examination invaluable in the diagnosis of obscure febrile conditions particularly in the differential diagnosis between pneumonia and acute appendicitis. Where no pneumococci are found in the direct smear, the child is not likely to be suffering from early pneumonia.

The illustrations clearly demonstrate the usual findings in an early severe pneumonia. In Figs. 2 and 4 the exudate is seen to be actually swarming with pneumococci. With a higher magnification the larger clusters of bacteria suggest colony formation. Few pus or epithelial cells are to be seen. Fig. 5 represents a sputum smear from an early Type II pneumonia with only a two-day history of onset and without any chest findings either by x-ray or clinical examination. This picture

precludes the idea that the organisms might have been coughed into the nasopharynx. Fig. 6 shows tubercle bacilli in sputum from an infant. This picture would indicate the efficiency of the laryngeal aspiration method of obtaining sputum.

Because we found the pneumococci particularly numerous in the nasopharynx in the early stages of childhood pneumonia, we feel that the nasopharynx is a breeding ground for pneumococci and is probably the source by which pneumococci reach the lung. Further investigation will have to be made to support this view.

SUMMARY

A new suction method of obtaining sputum from infants and children has been described.

With experience one is usually able on the first attempt to obtain sufficient sputum from either the larynx or the nasopharynx to carry out an examination by direct smear and typing by the Neufeld method.

The laryngeal method is recommended in cases of suspected tuberculosis, whooping cough, or pneumonia due to mixed infection, while sputum from the nasopharynx is ideal for typing pneumococci.

The nasopharynx has been suggested as a breeding ground for pneumococci and as the probable source by which pneumococci reach the lung in pneumonia of infants and children.

In obscure febrile conditions in which the diagnosis seems to lie between an acute appendicitis and pneumonia, the finding of large numbers of pneumococci in the nasopharynx before any definite physical findings in the chest can be recognized is an indication that the child is suffering from a developing pneumonia; the subsequent course of the disease supports this view. The possibility that the condition is pneumococcic peritonitis must not be overlooked.

THE RESULTS OF TYPING PNEUMOCOCCI FROM SPUTUM FROM 450 CASES OF PNEUMONIA AMONG INFANTS AND CHILDREN

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DURING the past year sputum from all the pneumonia cases admitted to the wards of the Hospital for Sick Children has been examined. The sputum was obtained in most cases from the nasopharynx by means of the suction method.[1] It was examined directly by stained smear and by the Neufeld technique for typing pneumococci. Further examination included the culturing of suitable particles on a blood agar plate and mouse inoculation. If no pneumococci were to be found directly in the nasopharynx, sputum was then obtained from the larynx, again by means of suction. We have found the nasopharyngeal secretions ideal for typing pneumococci in cases of early severe pneumonia in children, and where confirmation of the type of pneumococcus found in the sputum was possible by examination of either pleural exudate, blood culture, or post-mortem lung culture, this method has been found accurate in about 90 per cent of the cases. From Sept. 8, 1938, until June 8, 1939, sputum from 450 pneumonia cases has been examined. In each of these cases a clinical diagnosis of pneumonia was made by a member of the attending medical staff and checked by x-ray. No attempt was made to differentiate lobar from bronchopneumonia.

In addition, a special study was made of the cases of Type I pneumonia among children. During the winter months of 1937-38 our incidence of Type I pneumonia was 30 per cent, and of these about one-fourth developed empyema. This has already been observed by other authors.[2, 3] It was hoped that, by early diagnosis followed by prompt serum or chemical therapy, information might be obtained as to the means of prevention of this serious complication. These results have been tabulated and briefly discussed.

Table I

Showing the Incidence of Pathogenic Organisms in Pneumonia Sputa From Sept. 8, 1938 to June 8, 1939

	Cases of Pneumonia	Pneumococci	More than one type pneumo.	Strep. hemolyticus	Staph. aureus	B. influenzae
Under 2 yr.	186	141	32	49	49	22
Over 2 yr.	264	234	57	50	22	24
Total	450	375	89	99	71	46
		83.3%		22.0%	15.8%	10.2%

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RESULTS

Table I shows the incidence of the main pathogenic organisms found in the sputum from 450 cases. The pathogenic organisms other than pneumococci have also been recorded when they occurred in sufficient numbers to be a likely etiological agent of the pneumonia. Pneumococci were present in 375 (83.3 per cent) of sputa and of these 375 specimens, 89 (23.7 per cent) contained more than one type of pneumococcus in the same sputum. Of these 23.7 per cent with more than one type of pneumococcus, in half of them the extra type could be found by direct examination while in the other cases the extra type or types were picked up after passage through a mouse. Three types of pneumococci on direct examination were only found in one sputum, that of an infant. The problem of deciding which is the likely pathogen when two or more types of pneumococci are present in the same sputum may be very difficult. However, one of these types is usually virulent while any other type present is likely acting in the role of a mouth organism. For instance, if Type I, II, or V is found in a sputum, any other type also found in the same sputum can be ignored since these three types, in our experience, are always the cause of the pneumonia.

It is interesting to note the relatively high incidence of *Staphylococcus aureus* in the 0-2 year age group as compared to the 2 year and older age group. This will be reflected in the mortality table.

TABLE II

SHOWING THE RESULTS OF EARLY TYPE I PNEUMONIA CASES TREATED IN SERIES FROM OCT. 19, 1938 TO JUNE 8, 1939

GROUP	NO. OF CASES	EMPYEMA	% EMPYEMAS	SURGICAL DRAINAGE	DEATHS
Control	25	5	20.0	5	0
Serum treated	25	4	16.0	4	1*
Sulfapyridine treated	24	2	8.3	1	0
Total	74	11	14.9	10	1

*Died following a bilateral rib resection.

While the typing of pneumonia cases commenced Sept. 8, 1938, the treatment of Type I pneumonia cases in series did not start until October 19, partly due to the difficulty in obtaining sulfapyridine. After this period we were able to diagnose and treat serially 74 cases of early Type I pneumonia according to the following plan. The early Type I pneumonia cases were divided serially into three groups. Group 1 was used as a control group, receiving no serum or sulfapyridine. Group 2 received antipneumococcic rabbit serum. Group 3 received sulfapyridine. The other Type I pneumonia cases (21) not included in the series were those cases either with empyema on admission or with a history of pneumonia eight days or longer before admission. In addition, there were four cases which were not included in the series because of error in diagnosis on admission.

The results indicate a 20 per cent chance of a child with early Type I pneumonia developing empyema. This high incidence was only slightly lowered with serum but was considerably lower in the group treated with sulfapyridine. While this series is too small to arrive at any conclusions, still sulfapyridine seems to have lowered the empyema incidence. Based on this one ray of hope, future treatment should depend on either sulfapyridine alone or sulfapyridine in conjunction with serum therapy with a view to reducing the incidence of Type I empyema to a minimum.

The importance of this problem is indicated by the fact that from Sept. 8, 1938, there were 375 cases of sputa with pneumococci present of which 105 (28.0 per cent) were Type I. Of these 105 cases of both early and late pneumonia 29 (27.6 per cent) developed empyema. Also it should be stated that 80.6 per cent of the pneumococcic empyemas were Type I.

TABLE III

INCIDENCE OF IMPORTANT TYPES OF PNEUMOCOCCI OCCURRING SINGLY IN PNEUMONIA SPUTUM FROM SEPT. 8, 1938 TO JUNE 8, 1939

		I	II	III	IV	VI	XIV	XVIII	XIX	XXIII	UTP	OTHER TYPES
Under 2 yr.	109	3	0	6	3	6	12	6	14	6	17	36
Over 2 yr.	177	76	16	9	6	3	10	6	11	6	8	26
Total	286	79	16	15	9	9	22	12	25	12	25	62
%		27.6	5.6	5.2	3.1	3.1	7.7	4.2	8.7	4.2	8.7	21.7

Only the incidence of those types occurring most frequently and singly in pneumonia sputum have been included in Table III. The relative infrequency of Type I and II pneumonia among infants is in contrast with the higher types of pneumococci especially Type XIX. UTP refers to pneumococci which were untypable yet were bile soluble. In general Types I, XIV, XVIII, and XIX pneumococci were most common. Type VI was often associated with another type of pneumococcus, and its incidence is really higher than the above figure would indicate. The pneumococci occurring with other types in the same sputum could not be included in this table without sacrificing the percentage estimate.

TABLE IV

MORTALITY RATE OF PRIMARY PNEUMONIA OCCURRING IN THE 450 PNEUMONIA CASES

AGE GROUP	PNEUMOCOCCUS		MIXED		OTHER ORGANISMS		MORTALITY	
	CASES	DIED %	CASES	DIED %	CASES	DIED %	CASES	DIED %
0-1 yr.	41	14.6	50	28.0	30	40.0	121	27.5
1-2 yr.	32	3.1	23	8.7	12	8.3	67	6.7
2 yr. and over	170	2.9	63	3.2	29	10.4	262	5.5

In Table IV is shown the mortality rate per age group. A postmortem examination was obtained in 75 per cent of the deaths. In this table the pneumonia cases have been divided according to their probable bacterial etiology. "Pneumococcus" refers to all those cases of pneumonia with pneumococci as the sole likely cause of the pneumonia. "Mixed" refers to pneumococci plus another organism as the likely causative organism. The term "other organisms" refers to cases of pneumonia likely due to some organism other than the pneumococcus. The highest mortality occurred among the infants of 0 to 1 year in whom organisms other than pneumococci were the cause of death. In this age group 12, or 40 per cent, of the patients died, and of these 12 deaths, 7 (58.3 per cent) were due to *Staphylococcus aureus*, either solely or in combination with *Streptococcus hemolyticus* or *Bacillus influenzae*. The death rate was only 2.9 per cent for cases in the age group over 2 years when due to pneumococci alone. Note the rise in the death rate as other organisms are found along with the pneumococcus, but note that the highest mortality rate is found in the nonpneumococcus group. It is interesting to note that 27.5 per cent of the infants under 1 year of age died while only 6.7 per cent of the infants between 1 and 2 years died and 5.5 per cent of children in the age group over 2 years died.

SUMMARY

Pneumococci were present in 83.3 per cent of the sputa. The most common types were I, II, XIX, XIV, XVIII in children over 2 years of age, and Types XIX, XIV, and UTP (untypable pneumococci) were the most common in children under 2 years of age.

Of the patients with early cases of Type I pneumonia who received no specific treatment, 20 per cent developed empyema, while 16 per cent developed empyema with serum therapy and only 8 per cent with sulfapyridine.

It was found that the mortality rate was very high for infants under 1 year of age especially when the pneumonia was due either to the pneumococcus plus another pathogen or to an organism other than the pneumococcus.

Staphylococcus aureus was a cause of death in 58.3 per cent of infants under 1 year of age when the pneumonia was due to an organism other than pneumococcus.

REFERENCES

1. Auger, W. J.: J. PEDIAT. **15:** 640, 1939.
2. Nemir, Rosa Lee: J. PEDIAT. **13:** 228, 1938.
3. McClure, W. B.: Canad. M. A. J. **38:** 369, 1938.

INTRAMUSCULAR ADMINISTRATION OF ANTIPNEUMOCOCCAL SERUM IN INFANTS AND CHILDREN

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THE intramuscular administration of a single dose of antipneumococcal serum in the treatment of type-specific lobar pneumonia in childhood was attempted in an effort to obtain the advantages of serum therapy without the dangers and technical difficulty inherent in intravenous administration. This study covered a period from March, 1938, to March, 1939, and consisted of a total of 64 cases. Eighteen of these were infants (under 2 years of age), and 46 were children (over 2 years of age).

Secretion for typing was obtained mainly by means of a pharyngeal swab. Stomach washings were also used. In a few instances, mouse inoculation was necessary. Types were determined by means of the Neufeld reaction. We were able to type most of the cases 24 to 48 hours after admission.

Patients selected for treatment were those who appeared to be seriously ill; the milder cases were not treated. The amount of serum varied from 60,000 to 100,000 units for the infants and 80,000 to 200,000 units for the older children. All subjects were tested for sensitivity by means of the ophthalmic and cutaneous reactions. Most of them showed negative reactions. The positive reactors received a suitable dose of epinephrine with the serum. Seven of the subjects received horse serum, and all the rest received rabbit serum. Half of the serum was injected into the muscle of each buttock. There were no thermal reactions. Local pain and tenderness occurred in most of the cases, and in a few this was accompanied by swelling and redness.

Agglutinin titration was performed on many of these children, and although agglutinins appeared in almost all of them, they were always of low titer. The Francis test was much more satisfactory and was used whenever the specific soluble substance was available.

Finland and Brown[1] administered 30,000 units of Type I antipneumococcal horse and rabbit serum intravenously and intramuscularly to nonpneumonic adults. The intravenous group received a test dose of 2 c.c. followed in 2 hours by the full dose. The intramuscular group received the full dose into the buttock in one injection.

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They found that in intravenous administration, maximal mouse protection titers were reached 5 hours after the full dose was given. The maximal titers were maintained for 24 hours with horse serum and 48 hours with rabbit serum. Thereafter, they declined rather rapidly. In the intramuscular group, maximal titers appeared 48 hours after injection and maintained this high level for as long as 6 to 9 days with both horse and rabbit serum. It is to be noted that after the 5-hour period the intramuscular group approached the corresponding levels of the intravenous group. Titers in the intramuscular rabbit serum recipients were constantly higher than those in the horse serum recipients. Through the courtesy of Finland and Brown Chart 1 is shown.*

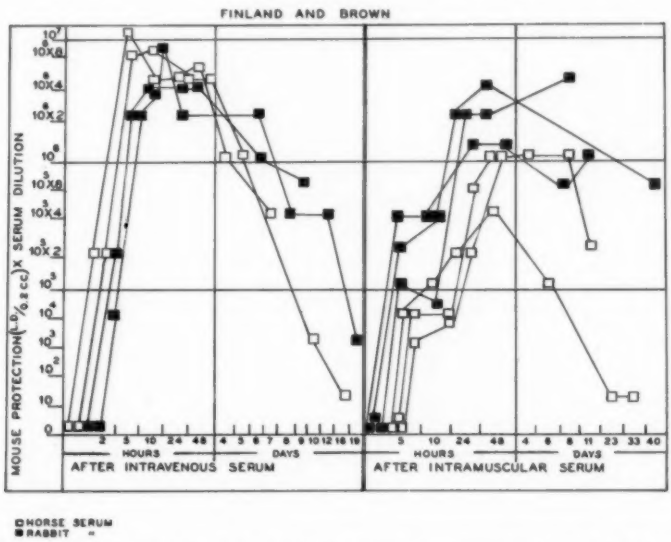

Chart 1.—Graph showing titers of circulating mouse protective antibody after injection of 30,000 units of Type I pneumococcal serums.

The cases recorded in Chart 2 illustrate temperature curves typical of this series and results obtained with the Francis test.

It will be observed that the temperature dropped to normal within 24 to 48 hours after serum administration in all of them. This temperature response was observed in all but one of our cases. In a few, there was a critical drop, but in the majority the temperature subsided by lysis. Coincident with the drop in temperature, there was a marked reduction in toxemia. Restlessness and irritability abated, and the cough became less troublesome. Food and fluid were taken in larger amounts with no ill effects. Most of the patients showed

*Chart 1 is reproduced from the *Journal of Immunology* through the courtesy of Finland and Brown and the Williams & Wilkins Co.

signs of resolution at the usual time, but in a few consolidation persisted for 3 or 4 days after the temperature subsided. The case of H. L., whose highest temperature was 102° F., might mislead one as to severity. However, he was one of our sickest pneumonia patients; his condition when he entered the hospital was most critical. The marked decrease in toxemia and his apparent improvement following the administration of serum was striking. It is our belief that the administration of a second injection of serum as shown in the cases of C. V. and R. R. was unnecessary, inasmuch as the Francis test was positive before the second injection was given. Clinical improvement in a few of our cases was not as prompt as in the others, and, since it was felt that inadequate dosage was responsible, more serum was given in an attempt to hasten recovery.

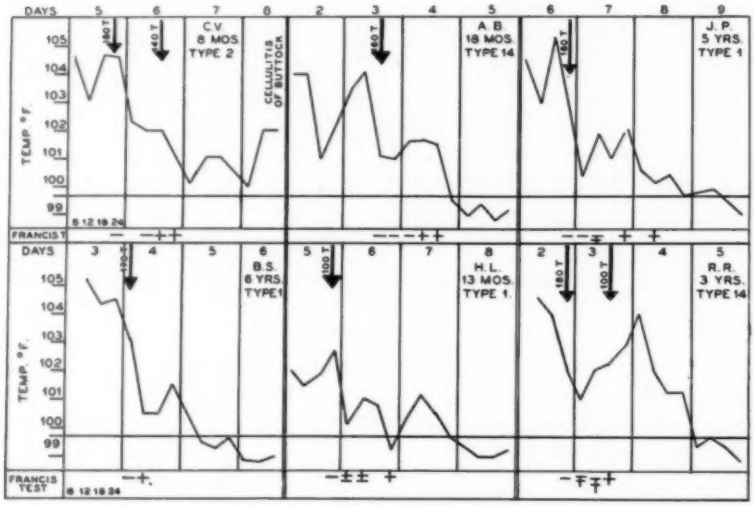

Chart 2.—Graph of cases illustrating typical temperature curves and results with the Francis test.

The Francis test was negative in all instances prior to serum administration. It was again negative 6 hours after serum injection, a plus-minus (erythema 1 cm. in diameter, no wheal) reaction was obtained in a few cases at the 6- to 12-hour period. With the exception of one case (Fig. 7), all patients on whom the test was performed showed a strongly positive reaction (erythema, wheal, and pseudopodia) eighteen to twenty-four hours after serum administration. The results of the Francis tests follow rather closely the mouse protection titers obtained by Finland and Brown. Francis[2] has shown that a positive cutaneous reaction to the specific soluble substance in Type I pneumonias was intimately associated with the presence of type-

specific antibodies in the patient's serum and that its appearance was invariably followed by recovery. He stated that "the mechanism of the positive skin test is closely related to that operative in recovery from pneumonia and is apparently the resultant of the antibody and tissue activity."

Chart 3, a composite chart of the cases of the 18 infants treated with intramuscular serum, shows (1) the type of pneumococcus, (2) duration of the illness before serum administration, (3) duration after serum administration, and (4) complications.

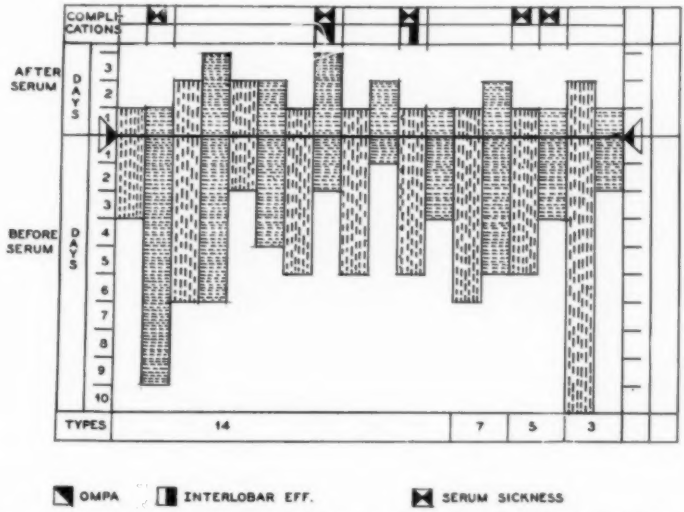

Chart 3.—Graph showing duration of illness before and after the administration of antipneumococcal serum to 18 infants.

Type XIV pneumococcus occurred in 12, or 66 per cent, of the infants. The duration of the disease before serum administration varied from 1 to 10 days. The average was 4.5 days. The duration after treatment varied from 1 to 3 days. The average was 1.5 days. The temperature dropped to normal in 10 of these infants in 24 hours. Six subsided in 48 hours, and 3, in 72 hours. Serum sickness occurred in 5 cases, or 28 per cent. Catarrhal otitis media was observed frequently but in only one instance terminated in suppuration. One infant (C. V., Chart 2) developed an abscess of one of the buttocks due to *Staphylococcus aureus*. Another developed an interlobar effusion which was absorbed spontaneously. There were no deaths.

Chart 4 shows the cases of 46 children treated with intramuscular serum. Type I pneumococcus occurred in 24, or 52 per cent. Four of them had bacteriemia. One of the other children ill with a Type V

pneumonia also had bacteriemia. Type XIV was the next most common and occurred in 6 cases, or 13 per cent. The duration of the illness before serum administration varied from 2 to 7 days. The average was 4 days. The duration after treatment was 1 to 3 days. The average was 1.5 days. The temperature dropped to normal in 25 of these children within 24 hours. Eighteen subsided in 48 hours, and 3 in 72 hours. Serum sickness occurred in 10 cases, or 21 per cent. Complications occurred about as frequently as in the infants. Two cases developed an empyema which required surgical drainage. One developed an interlobar effusion which was spontaneously absorbed. Four cases developed an acute purulent otitis media. There were no deaths.

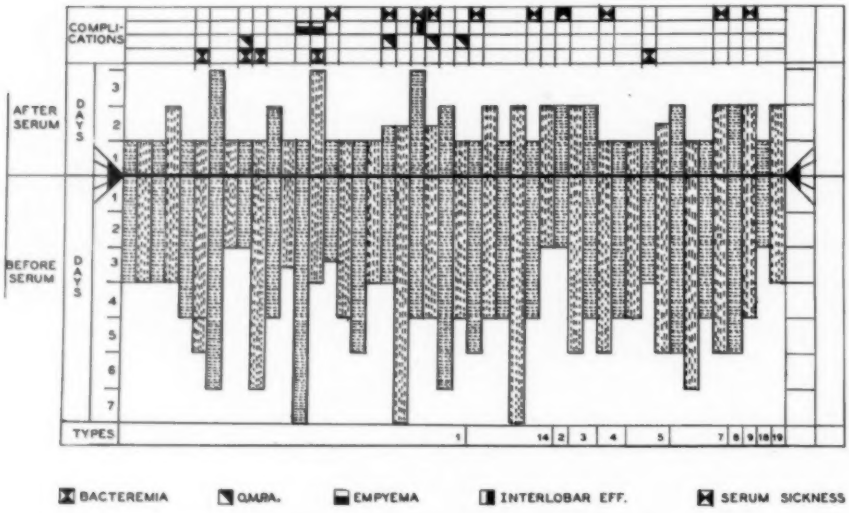

Chart 4.—Graph showing duration of illness before and after the administration of antipneumococcal serum to 46 children.

The differences between the serum-treated infants, 1938-1939, and the infants not treated with serum, observed at our hospital during the past ten years, 1928-1938, are shown in Chart 5. The duration of the disease before hospitalization and before serum administration was about the same in all the years and averaged 4.5 days. The average duration after hospitalization in the nonserum-treated infants was 5.7 days, while the average duration after serum therapy was 1.5 days, a reduction in morbidity of 4 days. There were no deaths in the serum-treated group, but in those who received only the usual supportive therapy, our average mortality was 12 per cent. There was a marked reduction in complications in the serum-treated infants. It is interesting to note that in some years all cases were complicated.

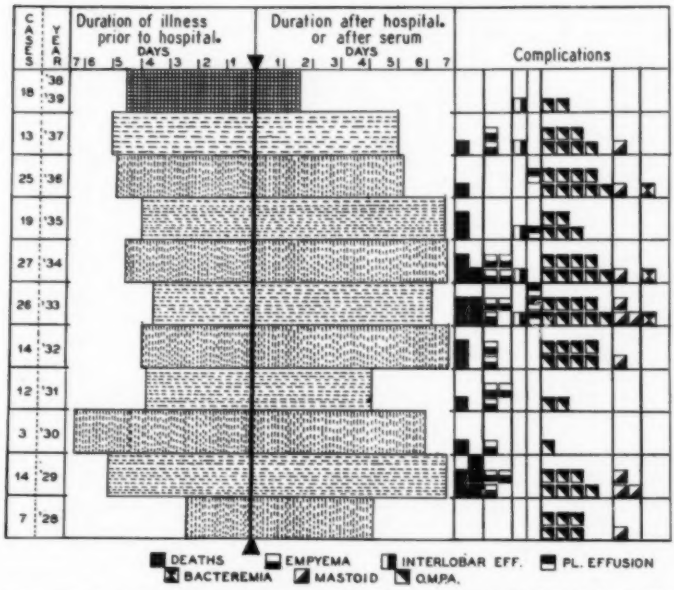

Chart 5.—Graph showing comparison of serum-treated infants (1938-1939) and infants not treated with serum (1928-1937).

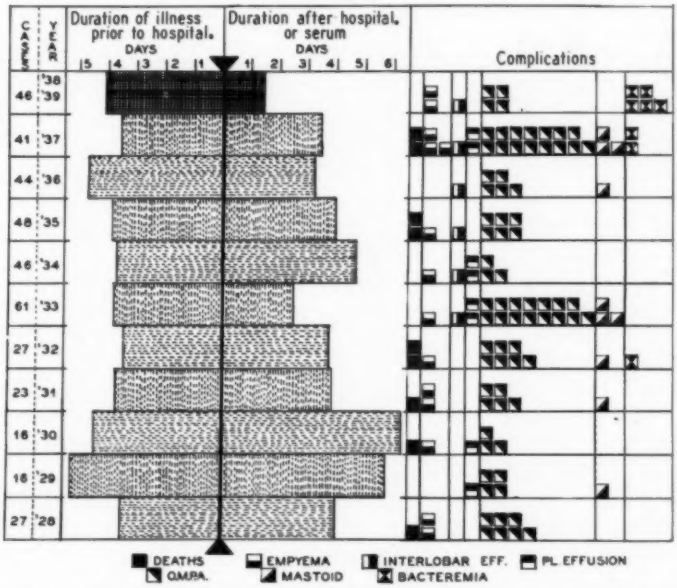

Chart 6.—Graph showing comparison of serum-treated children (1938-1939) and children not treated with serum (1928-1937).

Chart 6, a comparative study of serum-treated children (1938-1939) and children not treated with serum (1928-1938), similar to the study of the infants, shows much the same results but not to such a marked degree. The duration before hospitalization or before serum therapy was about the same in all the years and averaged 4 days. The average duration after hospitalization in the children not treated with serum was 4.25 days, while the average duration after serum therapy was 1.5 days, a reduction in morbidity of 2.75 days. There were no deaths in the serum-treated group; however, the subjects not treated with serum also showed a low mortality. The average was 2.5 per cent. There were no deaths in 1929, 1933, 1934, or 1936. Reduction in complications was not as marked as in the infants, but when one considers the fact that only the seriously ill patients were treated and that these included 5 patients with bacteriemia, the complications are much lower than one would expect them to be.

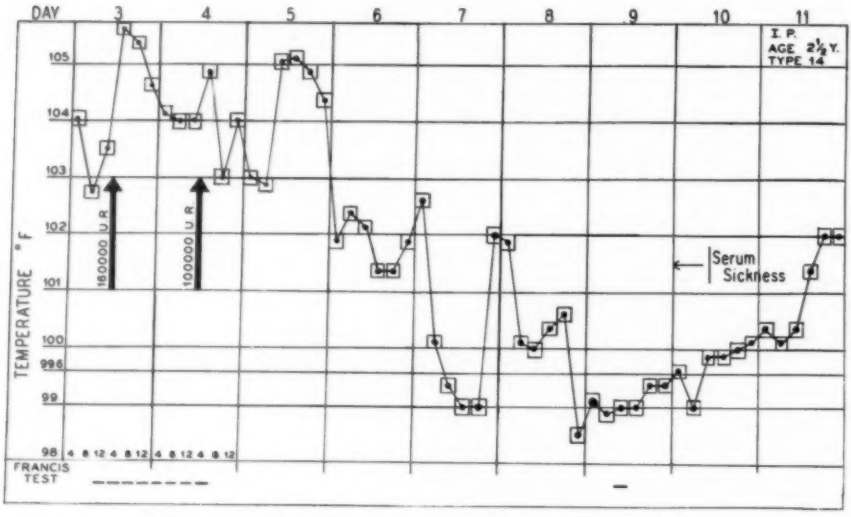

Chart 7.—Graph showing serum failure, Type XIV pneumococcus.

Chart 7 illustrates our only failure with serum therapy. This 2½-year-old girl came to the hospital on the third day of her illness. She was seriously ill. A diagnosis of lobar pneumonia involving the right upper lobe was confirmed by radiologic examination. In addition to her pneumonia, she had an acutely inflamed throat with a nondiphtheritic membrane covering the lower half of the right tonsil. Immediate typing showed a Type XIV pneumococcus. Type XIV rabbit serum, 160,000 units, was injected into the buttocks. After 24 hours, there was no change in her general status nor in the pharyngeal and pulmonary condition. The Francis test, performed every 4 hours,

remained negative. Another typing was performed with the same results. Feeling that the amount of serum given was inadequate, a second injection of 100,000 units was given. During the next 24 hours there was no change in the temperature curve and no relief of toxemia. There was no demonstrable improvement of the throat infection nor of the pneumonia. The temperature subsided by lysis on the eighth day of her illness. The Francis test, performed on the ninth day, was again negative. We are unable to explain this failure.

COMMENT

This study has impressed us with the value of antipneumococcal serum administered by the intramuscular route. The absence of any severe reaction speaks for the safety of this method. Clinically, the drop in temperature and the relief of toxemia, followed by a comparative well-being of the child, would tend to show that sufficient serum was absorbed from the muscle to account for the results obtained. The clinical observations are in keeping with the results of the Francis tests and with the mouse protection titers obtained by Finland and Brown. We are aware of the favorable reports from other parts of the country where only the usual supportive measures were carried out; however, when we compare our serum-treated cases with our nonserum-treated cases (1928-1938), the decrease in morbidity, mortality, and complications would seem to justify our belief.

CONCLUSIONS

1. A study of the intramuscular administration of type-specific antipneumococcal serum in the treatment of lobar pneumonia in 64 infants and children is reported.

2. The absence of any severe reactions shows this to be a safe route.

3. The decline in temperature and the relief of toxemia, followed by a comparative well-being of the child, tend to show that sufficient serum was absorbed to account for the results obtained.

4. It is our belief that, in infants and children ill with lobar pneumonia, the type of invading pneumococcus should be determined and antipneumococcal serum used intramuscularly in all who are seriously ill, particularly in those with bacteriemia.

REFERENCES

1. Finland, M., and Brown, J. W.: J. Immunol. 35: 245, 1938.
2. Francis, Thomas, Jr.: J. Exper. Med. 57: 617, 1933.

ICTERUS GRAVIS NEONATORUM

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A FAIRLY accurate conception of blood production from early fetal life through the period of transition, which begins when the newborn baby takes his first breath and ends when the blood picture becomes what is generally recognized as normal, has been made possible by numerous studies which have been conducted chiefly during the last two decades. Moreover, it has been observed that many extraordinarily interesting things occur during this period. The changes which take place may proceed in an orderly manner, in accordance with what the present state of our knowledge indicates is normal, or there may be interruptions in the normal sequence followed in hematopoiesis and hemolysis, for which we have yet to find entirely satisfactory explanations. During fetal life and for a short period after birth, it seems to be quite firmly established that the development of the erythrocyte takes place in several extramedullary centers of erythrogenic activity and is not wholly confined to the bone marrow, as it is in later life. These extramedullary erythrogenic centers are located chiefly in the liver and spleen, and to a lesser extent in the kidneys, pancreas, intestinal tract, adrenals, thymus, and gonads.[1-6] A short while after birth, these centers cease to function and hematopoiesis occurs entirely in the bone marrow. Under certain conditions, however, activity in the extramedullary centers may be continued or resumed. In order to understand these deviations from the normal sequence of hematopoiesis in early life, it seems desirable briefly to review the recognized changes which occur in the blood of the normal newborn infant.

Hematologic Characteristics of the Newborn Infant.—One of the first things with which we are impressed is that the color of the blood at birth is a darker shade of red than it is in later infancy and childhood. A large number of circulating erythrocytes and an increased hemoglobin of the blood content account for this color. This provides for an adequate maintenance of tissue respiration in the environment of low oxygen tension existing in intrauterine life. There has been, however, some variation reflected in the observations of different investigators concerning the number of erythrocytes in the blood in the first few weeks of extrauterine life, and more recent observations even tend to change the belief that a marked polycythemia exists at birth. The consensus[7, 8] at the present time is that the average lies between 5,000,000 and 5,500,000 and that the extremes vary between 4,000,000 and 9,000,000 per cubic millimeter.

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At birth the red cells show variations in size and shape, with a tendency to macrocytosis. The diameter approximates 8.5 micra or slightly above. Cells with a diameter above 10 micra are not infrequently found, but none have been reported above 12 micra in diameter. The variation in size usually disappears some time during the first week, but is practically always gone by the end of the second week. The average diameter after the first week gradually becomes less, reaching normal (adult) size by the sixth month.

The number of normoblasts which we may expect to find in the blood of healthy newborn infants has interested all investigators, and it has been almost universally accepted that as many as 5,000 per cu. mm. at birth is not to be considered an abnormal number. These immature red cells have disappeared usually by the second day and very rarely are present at the end of the first week. Nucleated red cells, younger than normoblasts, are always to be considered pathologic even at birth. Kato's studies[9] on 219 normal infants showed an average of 1.4 to 1.9 per cent reticulocytes at birth, with a maximum of 5.5 per cent and a minimum of 0.1 per cent during the first 36 hours, and a decrease below 0.5 per cent after the fifth day. These proportions remain for two or three weeks, then they begin to rise slowly, reaching a peak of 2 to 3 per cent at about the end of the second or during the third month.

Since the red cell at birth has a larger average diameter than it has in later life, the absolute hemoglobin content of the red cells is higher in the newborn than it is in any other period of life. The observations of those who have estimated the hemoglobin in the newborn vary considerably, but the plotted curves are strikingly parallel. In 1933 Helen Mackay,[10] as a result of her investigations on breast-fed and artificially fed London children, plotted a standard normal hemoglobin curve for the first year of life. Using Haldane's method, she found that the average hemoglobin content of the blood at birth was 143 per cent. This fell rapidly until it reached 75 per cent at three months and then rose to 80 to 90 per cent by the end of the first year.

The color index is usually high at birth, most often above 1.0, and it gradually falls until about three months, when it reaches a value that it generally maintains throughout infancy in normal cases.

The average number of leucocytes at birth is about 18,000 per cu.mm., but this varies considerably. They decrease rapidly during the first few days, but rise again to about 17,000 at twelve days. After this, the leucocyte count gradually falls during the first twelve years of life, when it reaches the normal adult level. An analysis of the differential leucocyte count indicates that polymorphonuclear neutrophils account for the increased total at birth. Furthermore, the secondary high figure which is reached at twelve days is due to an increase in lymphocytes. There is a shift toward immaturity at birth, so that myelocytes are frequently seen. This shift becomes less and disappears during the first week.

A considerable disparity of opinion exists with regard to the number of platelets in the blood of the newborn infant, but in general it may be said that, of all the cellular elements derived from the bone marrow, they are the only ones not increased in number at birth. Consequently, the normal adult number of 250,000 to 500,000 per cu.mm. is usually found. The bleeding and coagulation time are, as a rule, within normal limits.

As soon as the baby is born, it enters a period during which it must completely readjust itself to a new environment. As a consequence, most important changes take place in the blood, which lead to an establishment of an equilibrium between blood destruction and blood formation. The surplus of erythrocytes which is carried over from intrauterine life is no longer necessary in order to maintain adequate tissue respiration following the change from the environment of low oxygen tension *in utero* to a higher oxygen tension after birth. This is the most widely accepted explanation for the reduction in the number of erythrocytes and amount of hemoglobin in the period of readjustment after birth. This reduction in the number of circulating erythrocytes is brought about by a process of hemolysis, which in turn is also thought by many observers to account for the lowering of the amount of hemoglobin. Josephs,[7] however, is of the opinion that the reduction in the hemoglobin is due to a diminution in the rate of formation rather than to an increased destruction of blood. He bases this opinion upon the fact that until the hemoglobin has reached a certain low level, there is no evidence of blood regeneration even when iron is administered. Hampson's opinion,[11] that the hemolytic process is dependent upon an antihemolytic substance, will be discussed under etiology.

The changes which ordinarily occur after birth usually proceed in a sequence which is now regarded as physiologic. Included in these physiologic changes are icterus neonatorum and so-called physiologic anemia of the newborn. The preponderance of evidence seems to indicate that icterus neonatorum is due to an increased amount of bilirubin in the blood of the newborn infant as a direct result of the hemolytic destruction of the surplus erythrocytes. With the dissolution of the erythrocytes, hemoglobin is released and is taken from the blood stream by phagocytic cells contained within the liver, spleen, and bone marrow, and is split within these cells into bilirubin and a colorless iron-containing residue. The greater part of the bilirubin thus formed passes into the intestines where it is reduced to urobilinogen. A small quantity of the bilirubin is thought, however, to enter the blood stream directly. Most of the urobilinogen is believed to be reabsorbed from the intestinal tract and is returned to the liver through the portal circulation. Here it is reconverted into bilirubin, a small amount of which passes into the urine. The hemolytic process which occurs at birth causes such a marked overproduction of bilirubin in some instances that the liver is unable

to excrete the excessive amount. The bilirubin content of the blood then increases, and jaundice results. It is not possible, however, to exclude definitely some sort of functional incapacity of the liver as an additional factor. The icteric tint of the skin in this condition rarely if ever makes its appearance before the third or fourth day and usually subsides within eight to ten days. This is dependent, however, upon the amount of bilirubin in the blood stream. It is usually more marked and persists for a longer period of time in premature infants. Icterus neonatorum is rarely accompanied by any other detectable effects on the infant and requires no treatment.

The anemia occurring in the newborn period of adjustment, which has been designated physiologic anemia, is likewise inconsequential in its effect on the infant. Most observers agree that it should apply to the period when the hemoglobin is descending to its lowest level. It has been demonstrated that it cannot be influenced by any of the usual anti-anemic iron preparations.

In contrast to these two physiologic changes, certain pathologic conditions of the hematopoietic system may occur at or shortly after birth. Conspicuous in this respect is *icterus gravis neonatorum*.

ETIOLOGY

Many theories have been advanced in an attempt to assign a cause for icterus gravis neonatorum and to demonstrate its association with hydrops fetalis and congenital anemia of the newborn, and, as a result, it is generally believed at the present time that these three conditions, which have many points of similarity, have a common etiology. Therefore, the term "erythroblastosis fetalis" has been almost universally accepted to designate these three closely related clinical disorders. The evidence in favor of this view has been based upon many outstanding clinical, pathologic, and hematologic studies. Jaundice, which is so characteristic of icterus gravis, has not infrequently been found at birth in hydrops fetalis, while edema, which is such an outstanding feature of hydrops fetalis, has likewise been noted in icterus gravis, although it is usually localized and of a slight degree. In both, there are splenomegalia and hepatomegalia, a marked anemia, and frequently numerous immature red blood cells in the peripheral circulation (erythroblastemia), as well as evidence of a very active bone marrow and a marked extramedullary hematopoiesis, chiefly erythropoietic in character (erythroblastosis).

Stransky[12] is of the opinion that there are two rather distinct types of congenital anemia of the newborn. One type is characterized by a nonregenerative blood picture and presents but few, if any, features in common with icterus gravis. The other type, however, which is characterized by an embryonal blood picture, produces a strikingly similar

picture to icterus gravis in that there is often jaundice, hepatomegalia and splenomegalia, erythroblastosis, and erythroblastemia.

Diamond, Blackfan, and Baty[1] have clearly shown that in some instances after the jaundice has disappeared in those infants recovering from icterus gravis, the clinical and hematologic characteristics fulfill the diagnostic criteria of what is generally spoken of as congenital anemia of the newborn.

From time to time, certain observations have been made which prove very definitely that the similarities in these disorders, based on the clinical, pathologic, and hematologic findings, are subject to wide variations. For example, in each of the three conditions, cases have been reported in which there was little or no evidence of erythroblastosis. The occurrence of both hydrops fetalis and icterus gravis have been noted without the presence of nucleated red blood cells in the peripheral blood. Further, a marked erythroblastemia in icterus gravis has been found even when the red cells have not dropped below 4,000,000 per cu. mm. Finally, it is to be remembered, as pointed out by Pasachoff and Wilson,[13] that erythroblastosis is not confined to these conditions alone, as it sometimes occurs in congenital syphilis and sepsis of the newborn.

Darrow[14] has concluded that it is the familial association of these three conditions which constitutes the most convincing evidence for an etiological relationship. This familial tendency has been observed repeatedly, and it is not uncommon to find occurring in the same family, one child born with icterus gravis, another with hydrops fetalis, and still another exhibiting congenital anemia of the newborn. In addition, Macklin, Lamont, and Macklin,[15] in tabulating the incidence of erythroblastosis fetalis in twins, cite a case in which one of the twins was icteric and the other hydropic. It would be most difficult to explain this on a basis other than a common etiology.

No single theory, as will be discussed later, has adequately explained the underlying cause of icterus gravis neonatorum. There are, however, certain definitely established facts which are quite significant. As previously stated, this condition, in the majority of cases, shows a familial tendency. "Sporadic" cases have been reported in otherwise normal families, but, according to Josephs,[7] some of these may well be examples of the onset of a familial occurrence. The first born is nearly always spared and less frequently the second born, but once the disease occurs in a family, subsequent pregnancies almost invariably result in infants who are stillborn or affected with any one of the clinical types of erythroblastosis fetalis. In most instances, the infants are born at term, and there is apparently no relationship between the occurrence of the disorder and obstetric abnormalities. A normal pregnancy is usually noted, but a few observers, and particularly Rolleston,[16, 17] have reported the presence of various forms of toxemia of pregnancy. Simi-

larly, with the notable exception of Parsons,[18] who believes that a maternal anemia due to a deficient diet may, at times, cause an anemia in the offspring, most observers have found that anemia and nutritional disturbances do not exist in the mothers. Further evidence that the primary factor does not arise from the mother is to be found in those instances in which a pregnancy resulted in twins, one of whom was affected with erythroblastosis fetalis and the other was normal. Apparently the disease exhibits no racial tendency. Statistical studies, although few in number, offer evidence that icterus gravis is not as uncommon as was once believed. Clifford and Hertig[19] give an incidence of 1 in 340 newborn infants, and Andrew and Miller,[20] 1 in 490.

It is not within the scope of this paper to describe in detail the various theories which have been advanced to explain the cause of icterus gravis. Darrow,[14] in a recent publication, has made a very comprehensive and critical study of many of those which have been proposed.

The English investigators, including Parsons, Hawksley, and Gittins,[21] are strong advocates of the hemolytic hypothesis, thus assuming that the erythroblastosis and erythroblastemia are secondary to the hemolysis. They believe that it is by means of the erythroblastemia that the body meets the demand for "fresh" cells. On the other hand, Blackfan, Diamond, and Baty,[1] in this country, believe that the disease is due to a disturbance of the metabolism of the hematopoietic system resulting, first, in either a failure of maturation of the erythrocytes or in an overgrowth of immature forms of erythrocytes; second, in the delivery of immature nucleated erythrocytes in large numbers to the peripheral circulation; and third, in the increased destruction of the erythrocytes, including the nucleated forms. Hemolysis, according to this theory, is secondary to the erythroblastosis and takes place because the nucleated red cells are more prone to destruction than are the nonnucleated erythrocytes. No explanation has been offered as to the nature and cause of this primary disturbance of metabolism, nor has it ever been conclusively proved that immature red cells are more fragile than the nonnucleated forms. These authors, arguing against the idea that the hemolysis is primary, point out that in hydrops fetalis, where one finds the greatest amount of extramedullary hematopoiesis, hemolysis is much less evident.

Neither of these theories is completely satisfactory, for whether the hemolysis or the erythroblastosis is primary, the causal factor is still lacking. The English group have repeatedly stressed the possibility of a toxin as the cause of the primary hemolytic process. Parsons,[22] in the Schorstein lecture for 1938, in citing reasons for his belief that icterus gravis neonatorum is a hemolytic anemia, concludes that the occurrence of kernicterus with symptoms of the involvement of the basal ganglia and the development, three or four years later, of an impaired liver tolerance, as shown by intravenous glucose tolerance tests or of cirrhosis

hepatitis in certain cases, are evidence of the action of a toxin. This toxin, if it exists at all, must be one to which the mother is either wholly or partially immune.

Abt,[23] in 1933, proposed a theory based on the presence of erythroblastosis, but which he preferred to call "embryonal hematopoietic persistence." He compared the histology normally found in the hematopoietic system during the fourth or fifth month of gestation with that which is present in icterus gravis. The persistence of the extramedullary hematopoiesis he attributed to a defect in the anlage or in the germ plasm in the familial cases and to the influence of a toxin in early pregnancy in the sporadic cases. Josephs[7] contends that if the chief fault lies in a failure of hematopoiesis to develop beyond this fetal stage, one would hardly expect hematopoiesis to reach a normal level within three weeks of extrauterine life, after its failure to develop in the preceding four or five months.

Hampson,[11] in 1929, in an attempt to compare physiologic jaundice with icterus gravis, formulated the concept that hemolysis may be controlled in intrauterine life by a hormone or hormonelike substance produced in the mother and thus passed on to the fetus, and that this antihemolytic factor is produced by the infant itself in extrauterine life. The amount of hemolysis which normally takes place at birth is, according to this point of view, held in check by the antihemolytic substance. If this factor is absent or insufficient, the result is an excessive hemolytic process, with the production of an anemia and jaundice. The excellent results which he obtained from the use of blood serum in the treatment of icterus gravis were offered to substantiate the theory. Although the idea has never been disproved, the fact that but few report an equally remarkable success with the use of normal blood serum makes it unlikely. Prior to this, Ylppö[6] likewise had held that physiologic jaundice and icterus gravis were both due to the same factor: namely, the hemolysis of the excess red blood cells, which excess is brought about by the change in oxygen tension at birth. If this were true, the jaundice, which is so characteristic of icterus gravis, should not appear until after birth nor should the anemia occur until some hours after delivery. As is well known, both the anemia and jaundice are present at birth in a large number of cases of icterus gravis.

Hawksley and Lightwood[3] have offered the possibility of a Mendelian recessive characteristic as the causative factor, but, as Macklin has demonstrated, the incidence of the condition in a large family or in a series of families is too large to bear this out. Macklin[24] believes erythroblastosis fetalis to be dependent on the rise of a dominant mutation in the germ cells of one of the parents, the primary defect being the abnormal blood production, with hemolysis secondary. Darrow, however, points out that, if the disease were dependent on this factor, its occurrence would be distributed at random among the offspring, since it would

be largely a matter of chance whether any one child inherited the modified gene or not. This is not the case in icterus gravis.

Darrow[14] concludes that an antigen-antibody reaction is the best explanation of all these disorders. She states that in these clinical types of erythroblastosis fetalis, in which the symptoms indicate injury of the liver, passive sensitization to the hemoglobin of the red blood cells of the fetus has been transmitted from the mother through the placenta and through her milk after birth. She further states that in the aregenerative form of congenital anemia, it is likely that immunization rather than sensitization has taken place in the mother and has been transmitted as such to the child or that, in some cases, desensitization or possibly mitigation of the sensitization reaction has in some way been accomplished.

PATHOLOGY

An extensive extramedullary hematopoiesis is the principal and usually the most constant pathologic change observed in icterus gravis neonatorum. This extramedullary hematopoiesis is chiefly of the erythropoietic element and consequently has been designated by the term "erythroblastosis." The liver and spleen show the most marked involvement, but quite frequently the kidneys, adrenals, pancreas, thymus, and lymphatic glands also have been found to be centers of active blood formation. In the very severe cases, the microscopic picture which is produced by this excessive amount of hematopoiesis is strikingly similar to that normally observed in a four- or five-month fetus. Granulopoiesis occurs as well as erythropoiesis, but to a less pronounced degree. It is to be recalled that extramedullary hematopoiesis is occasionally present in the normal newborn, but occurs more frequently and with greater intensity in premature infants. In any event erythroblastosis is usually much more widespread in icterus gravis neonatorum. Gross examination at autopsy usually reveals petechial and ecchymotic hemorrhages in the skin, mucous and serous membranes, in addition to a generalized yellowish coloration of the various organs and serous surfaces. Pallor of the organs, in spite of their being bile stained, is often quite evident.

Liver.—This organ is enlarged to two or three times its normal size, and this is due primarily to the presence of a great number of blood cells developing between the columns of liver cells and within the capillaries. The immature red blood cells predominate in these hematopoietic islands. The normal histology of the liver may be considerably altered because of compression and narrowing of the columns of parenchymatous cells by the tremendous number of young blood cells. In some areas, the liver cells may actually be replaced by these hematopoietic aggregations. The immature granulocytes seem to accumulate in the portal tract and vessels. Notwithstanding the usual observation that erythroblastosis is a conspicuous pathologic feature of icterus gravis, instances have been recorded in which there were few if any areas of active blood formation in the liver.

The polygonal cells themselves exhibit various degrees of degeneration, some progressing to complete atrophy, and many of them contain bile pigment and hemosiderin, as do the bile canaliculi and the Kupffer cells. The bile capillaries are frequently distended with bile and occasionally present the so-called bile thrombi. In 7 out of 9 infants who lived for 5 weeks or longer, Hawksley and Lightwood[3] noted the development of a fine fibrosis among the polygonal cells of the atrophic areas and in the neighborhood of the portal tracts.

Spleen.—The spleen is likewise tremendously enlarged and congested and, as in the liver, numerous areas of hematopoietic activity can be demonstrated. Phagocytic cells are quite profuse and contain bile pigment and hemosiderin. Degenerative changes of the parenchyma have not been observed. Hawksley and Lightwood[3] found evidence of fibrosis in 4 cases of their series, in 3 of which the reticulum showed increased density and staining affinity.

Heart.—The heart is occasionally larger than normal; this is the result of both hypertrophy and dilatation. These findings, in addition to an edema of the muscle bundles, which has rarely been reported in icterus gravis neonatorum, are more characteristic of hydrops fetalis. Petechial hemorrhages are not uncommonly found in the epicardium.

Bone Marrow.—The bone marrow in most instances shows a pronounced hyperplasia of all of the hematopoietic elements. Diamond, Blackfan, and Baty,[1] however, noted a diminution in the number of megakaryocytes.

Kidney.—Pathologic changes, which have been observed in the kidneys, include the deposition of hemosiderin and bile pigment in the epithelial cells of the tubules. Infrequently, the parenchymatous cells undergo degeneration. The glomeruli are generally not involved. As has been previously stated, hematopoiesis may be quite active in this organ.

Lungs.—Hemorrhages, varying considerably in extent, have been repeatedly found in the lungs at autopsy. In several instances, hemorrhage involving a whole lobe has been present. Bronchopneumonic changes, as a terminal pathologic feature, are sometimes noted.

Central Nervous System.—Careful analysis of the pathology which may occur in the central nervous system has resulted in several interesting findings. The brain most often exhibits a striking pallor. In a relatively small number of cases, a definite icteric color of the brain tissue itself is observed. Schmorl[25] has divided this icteric staining of the brain into two groups: the first type presents a diffuse icterus, which apparently is not bound to any structural elements and which is due most probably to imbibition of the bile pigment; in the second group, the icterus is definitely localized in the nuclear areas and has been termed kernicterus by Schmorl. He found this sharp localization of pigment in

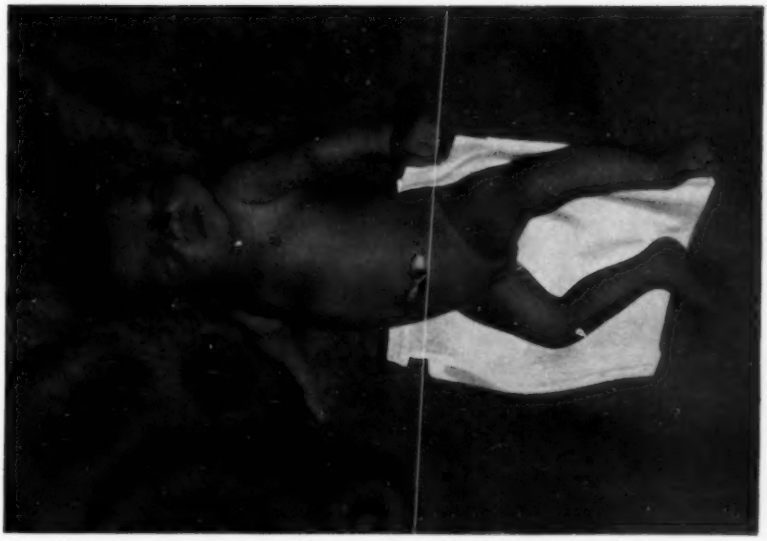

Fig. 1—Color of skin in icterus gravis neonatorum.

Fig. 2—Extent of splenomegalia and hepatomegalia.

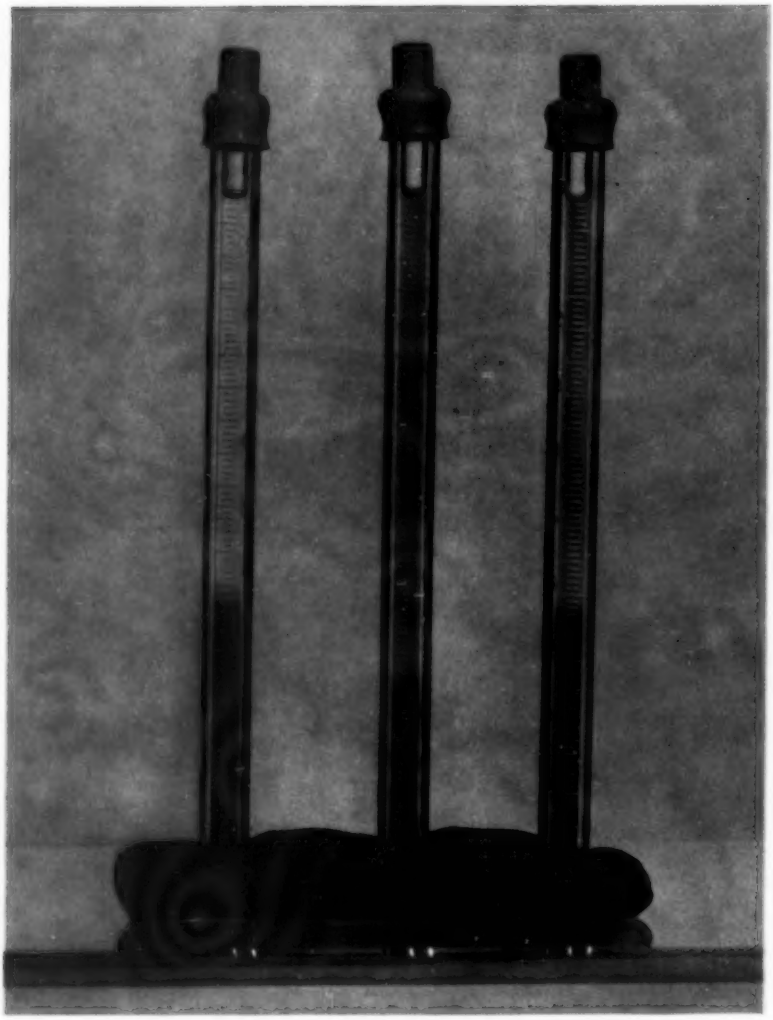

Fig. 3—(A) Packed cells and serum of normal newborn baby.

(B) Icteric serum and decrease in packed cells in icterus gravis neonatorum.

(C) Increase in packed cells and change in color of serum after transfusion.

6 out of 120 cases of jaundice in the newborn. Zimmerman and Yannet[26] state that this bile staining of the brain tissue occurs in none of the other varieties of jaundice in the newborn. It has not been demonstrated in adults. However, intracranial hemorrhage is apparently a more frequent occurrence than kernicterus. Hawksley and Lightwood[3] found subdural and cortical hemorrhages in 6 of their 18 cases.

CLINICAL FEATURES

The most outstanding and characteristic sign of icterus gravis neonatorum is the jaundice which is present at birth or very shortly thereafter and which may rapidly increase in intensity. Occasionally, the jaundice is not detectable until thirty-six to forty-eight hours after birth. In addition to the distinctive color of the skin, the amniotic fluid and the vernix caseosa may also be of the same yellowish hue. Abt[23] explains this discoloration of the vernix and the amniotic fluid as being due to the excretion of bile pigmented urine in utero. Some idea may be gained of the appearance of the skin in a typical case of icterus gravis neonatorum in Fig. 1 (Case 1), in which the color is accurately recorded on a kodachrome film. An examination of the conjunctiva, the mucous membrane of the buccal cavity, and the sclera may also reveal a pronounced icteric tinge. In those cases which recover, the jaundice gradually disappears, usually taking from 2 to 3 weeks to disappear completely, and rarely as long as 2 months. A marked pallor of anemia is observed as the icterus fades.

The next most important sign of icterus gravis neonatorum is a marked enlargement of the liver and an even greater enlargement of the spleen. This is illustrated in the outlines of the liver and spleen in Fig. 2.

Edema, although not nearly so characteristic as in hydrops fetalis, may be present and involve for the most part the eyelids and the extremities. Petechiae and at times widespread ecchymotic hemorrhages may occur. A hemorrhagic tendency with bleeding from the umbilical stump and from the gastrointestinal tract is occasionally present. The infant may or may not have an increased temperature. Drowsiness, from which it may be difficult to arouse the child, is common. Involvement of the central nervous system is not infrequent and, in addition to the drowsiness previously mentioned, neurologic signs may include convulsions, spasticity, increased reflexes, and occasionally opisthotonos.

Bile pigments and occasionally bile salts are found in the urine. As a rule, the feces are well colored with bile pigment, which may be in excess. Sometimes, the stools may be pale or colorless for the first few days after birth. When this occurs, we are justified in suspecting congenital obliteration of the bile ducts, but in icterus gravis the stools never remain pale for any length of time.

The changes which occur in the peripheral blood in icterus gravis neonatorum provide a striking contrast to the hematologic characteristics

of the normal newborn infant. One of the most marked deviations from the normal is the profound and severe anemia which is usually present in this condition. Total red blood cell counts as low as 500,000 per cu. mm. have been reported. The anemia is of the hyperchromic macrocytic type. The hemoglobin, although of a low value, is decreased proportionately less than the number of circulating erythrocytes. This accounts for the color index being in most cases greater than 1.0.

The most outstanding change in the blood picture is observed in a stained smear of the circulating blood, wherein an abnormally large number of immature nucleated red blood cells are found. Their number frequently exceeds 50,000 per cu. mm. The normoblast, with its pyknotic nucleus, is the most commonly encountered type of these young forms, but the erythroblast and sometimes the megaloblast may be seen. These cells gradually disappear, if the infant recovers, but may continue to be found in abnormal numbers as long as two weeks after birth. Reticulocytes are numerous and anisocytosis, poikilocytosis, and polychromatophilia are noted.

The number of leucocytes is invariably elevated, and this is due chiefly to an increase in the number of granulocytes. Immature leucocytes, predominantly of the granulocytic series, are often observed, but myelocytes and myeloblasts rarely form more than 5 per cent of the total white blood cell count. Diamond, Blackfan, and Baty,[1] in their cases, observed young forms of lymphocytes and monocytes in addition to immature granulocytes, but this has not been recorded by others. As recovery takes place, there is a rise in the number of eosinophils. This phenomenon, as has been pointed out by several investigators, is not an uncommon occurrence in most hemolytic anemias during the period of recovery.

In some instances, there is a reduction in the number of platelets, but, because many cases have shown a normal number, this decrease cannot be considered as a constant finding in icterus gravis neonatorum. The bleeding and coagulation times have been found to be normal or increased, and here again there is no unanimity of opinion.

The icterus index is always high. This may be visualized by the supernatant serum in the tube *B* in Fig. 3 (Case 1), as compared with the supernatant serum in the tube *A*, which illustrates the degree of bilirubinemia which may be expected in a normal newborn infant of the same age. The tube *C* illustrates results obtained following a transfusion.

The indirect van den Bergh is sometimes positive, but most commonly the test becomes biphasic from damage to the liver cells and obstruction of the bile ducts. The fragility test in our cases shows but little if any deviation from the normal resistance to hypotonic saline solutions.

DIFFERENTIAL DIAGNOSIS

Differentiation of icterus gravis neonatorum from those conditions which may exhibit one or several similar signs and symptoms, is fre-

quently a difficult task. Icterus neonatorum, prematurity, sepsis, congenital syphilis, congenital obliteration of the bile ducts, and congenital acholuric jaundice may be accompanied by either an erythroblastosis and/or an erythroblastemia or a jaundice, and occasionally all three features may be present.

Simple icterus neonatorum, in contrast to icterus gravis neonatorum, usually has its onset about the third day after birth and is not associated with a severe anemia, hepatomegalia, or splenomegalia. Although an erythroblastemia may be observed, the number of nucleated red blood cells, as previously described, rarely exceeds a maximum of 5,000 per cu. mm., and they disappear completely from the peripheral circulation in most instances within two to three days.

On the other hand, the following diseases of the newborn, when associated with simple icterus, must be considered, for not infrequently they produce signs suggestive of icterus gravis neonatorum.

The onset of *hemorrhagic disease of the newborn* usually coincides with the onset of physiologic icterus. Moreover, the anemia resulting from the blood loss is sometimes quite profound, but a splenomegalia and hepatomegalia are not as a rule present.

If physiologic jaundice occurs in an infant who has edema, enlargement of the liver and spleen and a cardiac murmur, real difficulty is encountered in distinguishing between a diagnosis of *congenital heart disease* and icterus gravis neonatorum. Usually the absence of a severe anemia and a negative family history will aid in ruling out icterus gravis.

Finally, *intracranial hemorrhage*, which manifests itself during the period of greatest intensity of simple icterus, must be considered in the differential diagnosis. Here the normal blood picture without an enlargement of the liver and spleen would be helpful in eliminating the possibility of icterus gravis.

Excessive hemolysis, which is not uncommonly associated with *prematurity*, may cause some confusion in those cases of icterus gravis neonatorum occurring in premature infants. Reference to this fact has already been made, and we need only add that if the jaundice is due to this simple excessive hemolysis, there is often little if any enlargement of the spleen, and the infant does not appear as ill as those who have icterus gravis.

Sepsis of the newborn, most frequently arising from an infection of the umbilical stump, should always be excluded as a possibility. The history of an antecedent infection and the fact that the jaundice developing as a result of sepsis is usually not noted until several days after birth are important differential features. A positive blood culture may be demonstrable in a few of those cases of icterus gravis which develop a terminal infection and, therefore, would not be helpful in a differential

diagnosis. Similarly, a "picket fence" temperature curve is not necessarily diagnostic of sepsis of the newborn.

Congenital syphilis has been definitely shown to be one of the causes of a marked icterus and of an erythroblastosis and erythroblastemia in the newborn. In addition, hepatomegalia and splenomegalia complete a clinical, pathologic, and hematologic picture which very closely resembles icterus gravis. In such cases, a history of syphilis in the mother, a positive Wassermann in the baby, and a roentgenologic demonstration of syphilitic changes in the long bones often constitute the only distinguishing points.

In *congenital obliteration of the bile ducts*, the changes characteristic of icterus gravis in the peripheral circulation are but seldom if ever observed. The jaundice makes its appearance most often after the second or third week, and the continuous passage of acholic stools is pathognomonic.

Congenital acholuric jaundice is excluded on the basis of a normal fragility of the red blood cells to hypotonic saline concentrations and by a negative family history.

PROGNOSIS

It is usually stated that the mortality in icterus gravis neonatorum is approximately 80 per cent, regardless of treatment. In most of those who recover, the blood picture as well as all of the physical changes which have taken place, return to normal. In some, however, who apparently recover, mental deficiency and spastic diplegia may occur at a later date as a result of intracranial hemorrhage or kernicterus. When death takes place during the period when jaundice exists, it is usually due to the anemia, hemorrhage, toxemia, convulsions, or medullary failure, while death from intercurrent infection is more common as the jaundice is subsiding.

On the basis of the finding of fibrosis in the liver by some observers, as well as the demonstration of an atrophic cirrhosis in children who were known definitely to have had icterus gravis, it is now generally believed that at least one type of idiopathic juvenile cirrhosis may be traceable to the changes brought about by this disease.[27, 28] Moreover, when it is considered that kernicterus may be associated with, and idiopathic cirrhosis of the liver may follow, icterus gravis neonatorum, the belief that hepatolenticular degeneration, which is characteristic of Wilson's disease, is in some way caused by icterus gravis neonatorum, seems to be justified.[3, 29] An attempt has been made to connect certain diseases of the spleen in later childhood with icterus gravis. The results of these studies at the present time, however, are too indefinite to assume that a relationship exists.[30]

Hawksley and Lightwood[3] have recorded cases of icterus gravis neonatorum in which apparent recovery had taken place, but in which

sudden recrudescences occurred with a return of the jaundice and all of the other characteristic signs and symptoms.

TREATMENT

Treatment is, for the most part, unsatisfactory, and repeated transfusions are the most hopeful therapeutic measures. It is believed, however, that transfusion is only a form of substitution therapy, supplying as it does sufficient erythrocytes to maintain adequate tissue respiration until normal hematopoiesis is established. Every effort should be made to prevent the occurrence of an intercurrent infection in the infant. Fluids should be administered to prevent, or if already present, to overcome, dehydration and demineralization. Glucose should be supplied so that the glycogen reserve of the liver will not be depleted.

CASE 1.—The patient, a white female, was born about 1 A.M. on Jan. 13, 1939. She was seen approximately eighteen hours after birth by one of our senior students, who asked that we see the baby with him because of the presence of a marked jaundice.

Low forceps and episiotomy had been performed in the delivery of the patient, but labor was in no way difficult. The membrane had ruptured several hours before the arrival of the obstetrician, so that accurate information as to whether or not the amniotic fluid was yellow could not be obtained.

This was the mother's second pregnancy, the first having resulted in a normal baby who developed normally. The mother attended the Prenatal Clinic, and her pregnancy was uncomplicated, with the exception of a slight amount of uterine bleeding, which occurred on November 16, and which was quickly checked. Three Wassermann tests on the mother gave negative results.

Physical Examination.—The patient was a well-developed, well-nourished, white female infant, weighing 7 pounds. She appeared to be quite drowsy, the usual stimuli giving rise to but little reaction. The skin was of a deep orange-yellow color. In several areas, the vernix caseosa was still present, and on removal with a cloth, was found to have a golden yellow color. The spleen was greatly enlarged, extending to the iliac crest and almost to the midline. The liver, likewise, extended almost to the crest. The two organs practically filled the abdominal cavity. There was a slight degree of edema of the upper and lower eyelids. Reflexes were distinctly sluggish. No petechiae were observed, and no bleeding from the gastrointestinal tract or the umbilical stump occurred.

Progress.—Immediately after the baby was seen in the home, she was sent to the hospital, where, on the following day, a direct transfusion of 50 c.c. of whole blood was given. Death came rather suddenly six hours after the transfusion.

Laboratory Data.—The laboratory findings in this case are given in Table I with those of Cases 2 and 3.

AUTOPSY

General Body Description.—The body was that of a well-developed, well-nourished, white female child, who weighed 7 pounds and whose length was 20 inches. The skin was of a deep yellow color, as were the sclerae and buccal mucous membrane, but no petechiae were observed. The abdomen was protuberant. The umbilical stump was well tied and presented no inflammatory process. A small incision was noted near the internal malleolus of the right ankle.

Peritoneal Cavity.—The usual midline incision was made and the peritoneal cavity exposed to view. The intestines were moderately distended and yellow in color, as was also the abdominal fat. All the organs were noticeably bile stained. The liver was markedly enlarged, extending 4 cm. below the costal margin. The spleen, likewise, was enlarged to approximately four times its normal size. All the abdominal viscera were in their normal positions and presented no disarrangement.

Thoracic Cavity.—The sternum was removed in the usual manner and both pleural cavities exposed to view. There was no fluid or inflammatory reaction in either pleural cavity.

Heart.—The pericardium was opened, and a small amount of clear, deep yellow fluid was found to be present. The heart was removed and examined, and no gross abnormalities of any character were noted.

Lungs.—The *right* lung measured 9½ cm. in length, by 4½ cm. in width, by 2 cm. in thickness, and weighed 22 gm. The lung was fully expanded and showed some decrease in crepitation, due to a marked degree of congestion and numerous hemorrhages. The hemorrhages were on the surface, as well as deep in the parenchyma of the lung, and varied in size from a small pinhead to some measuring 4 to 5 mm. in diameter. These areas were well defined and gave the lung a speckled appearance.

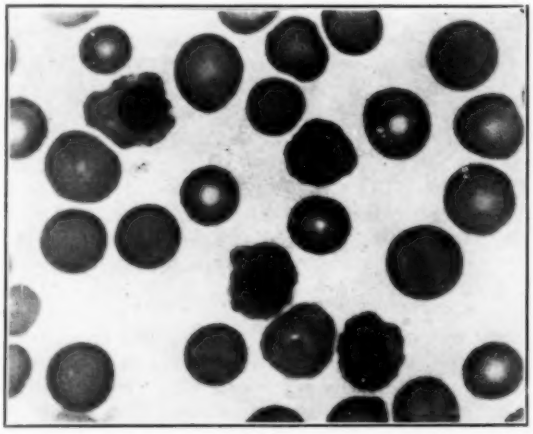

Fig. 4.—Stained blood smear, Case 1, showing immature red blood cells and macrocytosis. (Oil immersion.)

The *left* lung measured 9½ cm. in length, by 4½ cm. in width, by 2 cm. in thickness, and weighed 20 gm. The left lung was similar to the right in all respects.

Liver.—The liver measured 14 cm. in length, by 8 cm. in width, by 4 cm. in thickness, and weighed 136 gm. The outer surface was smooth and regular, and of a dark reddish brown color. The organ was somewhat less friable than normal and sectioned with slightly increased resistance. The cut surface was congested and of a similar dull reddish brown color.

Spleen.—The outer surface of this organ was smooth, regular, and of a dark steel-blue color. It sectioned with increased resistance, and the cut surface showed a moderate amount of congestion and was dark brown in color. The Malpighian corpuscles were not noted. The spleen measured 9 cm. in length, by 5½ cm. in width, by 3½ cm. in thickness, and weighed 42 gm.

Adrenals.—The adrenals were removed and examined. They showed no gross abnormalities.

Kidneys.—Both the right and left kidneys were normal in size and contained numerous fetal lobulations, but other than this, no abnormalities were present. The cut surface showed the cortex and medulla to be well demarcated; the cortex measured approximately 3 mm. in diameter, and was regular in outline. Both kidneys were moderately congested. The *right* kidney measured 5½ cm. in length, by 3 cm. in width, by 1½ cm. in thickness, and weighed 11½ gm. The *left* kidney measured 5 cm. in length, by 3 cm. in width, by 1½ cm. in thickness, and weighed 10 gm.

Pancreas.—The pancreas was normal in size. On gross examination, nothing unusual was found.

Gastrointestinal Tract.—The gastrointestinal tract when removed presented no abnormalities other than a generalized greenish yellow discoloration.

Genitals.—The uterus, tubes, and ovaries were in their normal positions, and were normal.

Bladder.—The bladder was normal in size. The urachus was present and patent, extending up to the umbilicus.

Culture From Spleen.—Negative after forty-eight hours' incubation.

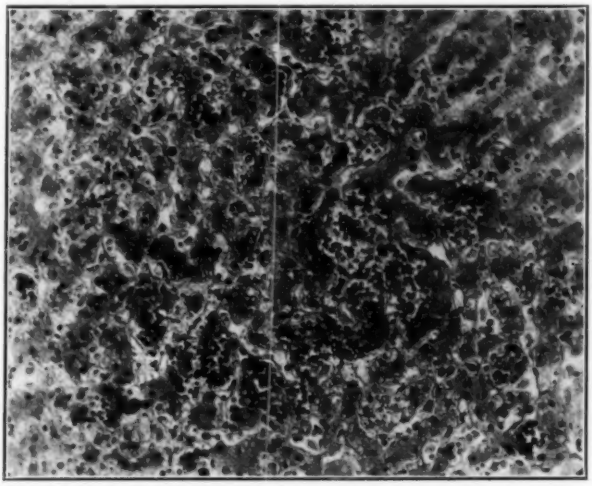

Fig. 5.—Section of the liver, Case 1, showing numerous islands of hematopoietic activity. (High-dry power.)

MICROSCOPIC FINDINGS

Lungs.—Many areas of hemorrhage were present, and in other areas an early bronchopneumonic process was apparent. The remaining alveoli were markedly emphysematous.

Pancreas.—The sections showed nothing of a diagnostic significance. The stroma was edematous and congested. In the stroma of areas from the tail of the pancreas, great aggregations of nucleated cells, chiefly of the erythroblastic type, were noted.

Adrenals.—There were a few aggregations of nucleated cells in the cortex. The cortical epithelium showed varying degrees of parenchymatous and hydropic changes. The medullary substance was narrowed.

Kidneys.—Nothing of diagnostic value was shown in the kidneys.

Spleen.—This organ was made up of markedly congested sinusoids filled with a variety of nucleated cells, many of which were of the erythroblastic series. The

lymph follicles were represented by a very few lymphoid cells. Many endothelial cells were noted in the pulp and sinusoids, some of which contained bile pigment.

Liver.—The sinusoids were crowded with nucleated cells, the majority of which were immature red blood cells. A few myelocytes were noted here and there in the sinusoids. The hepatic cells generally were granular and many of them contained fat droplets. The general histology of the organ was markedly distorted. No fibrosis was demonstrated.

Thymus.—Nothing of diagnostic significance was shown in this organ. Many nucleated cells were observed in the stroma and vessels of the thymus.

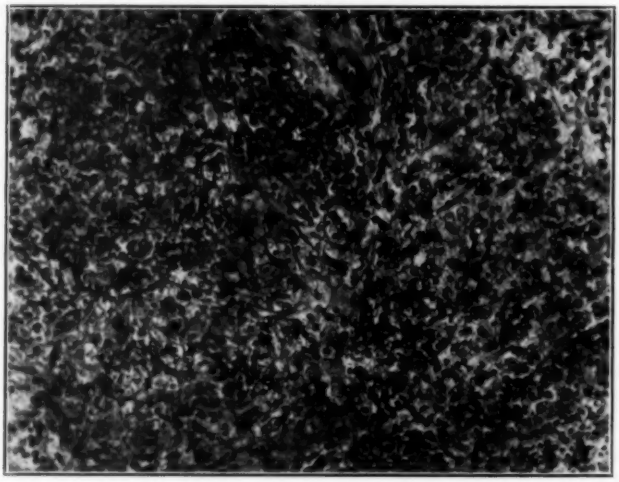

Fig. 6.—Section of spleen, Case 1, showing numerous islands of hematopoietic activity. (High-dry power.)

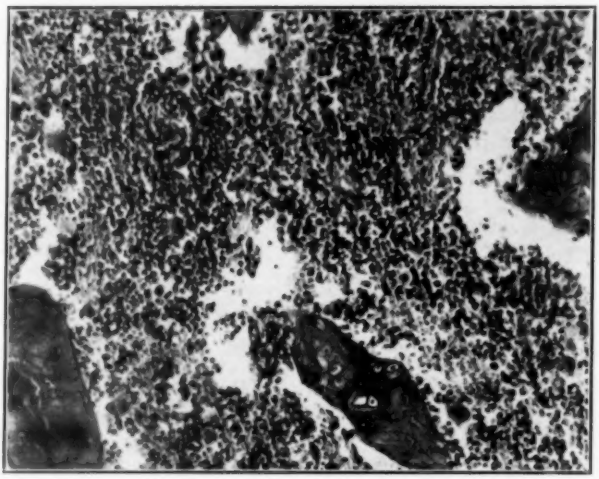

Fig. 7.—Section of bone marrow, Case 1, showing the marked hyperplasia, particularly of the erythroblastic element. (High-dry power.)

Sternal Marrow.—The bone marrow was exceedingly hyperplastic for all the hematopoietic elements, and immature red blood cells were particularly numerous. A large number of giant megakaryocytes were seen.

CASE 2.—A colored, male newborn was first seen by us on Jan. 21, 1939, approximately 48 hours after birth. Intense jaundice has been observed for the first time on the preceding day.

Delivery of the patient had been spontaneous, and the baby cried immediately after birth. The obstetrical resident, when questioned, stated that he did not find the baby jaundiced at birth nor was the amniotic fluid of a yellow color.

The mother had had four pregnancies before the birth of the patient: the first child died at 2 weeks of age, cause unknown; the second is living and well; the third died when 3 days old, of what the mother called "yellow jaundice"; the fourth child has been well since birth. The mother attended the Prenatal Clinic for each of her pregnancies and apparently no complications developed during the course of any one of them. Her Wassermann reaction had always been negative. No member of her or of her husband's family has ever given birth to jaundiced infants.

Physical Examination.—The baby appeared to be well developed and well nourished and weighed approximately 6½ pounds. The skin was intensely icteric, almost of a saffron color. The sclerae showed a similar discoloration. There was no evidence of pallor, most probably because of the deep jaundice. Breathing was rapid and shallow. Breath sounds were absent over both lung bases posteriorly. The abdomen appeared quite distended. The spleen was palpably enlarged, extending to just below the umbilicus in the midline. The liver was likewise enlarged, being palpated about four fingerbreadths below the costal margins. Reflexes were active, but not unusually so.

Blood was collected for study and for typing. Immediately after withdrawing the blood, 15 c.c. of whole blood was injected into the gluteal muscle, the mother being used as the donor. Several hours later, an indirect transfusion of 45 c.c. of citrated blood was given. A slight degree of bleeding occurred from the penis following the transfusion. Oxygen was administered continuously, and 5 per cent glucose and normal saline were given by hypodermoclysis. The patient expired about three hours after the transfusion.

AUTOPSY

General Body Description.—The body was that of a well-developed and well-nourished, colored male child, measuring 19 inches in length and weighing 7 pounds. The skin was very yellow. The conjunctivae and sclerae were likewise icteric. The cord had not yet dropped off. There was evidence of hemorrhage from the penis.

Peritoneal Cavity.—The subcutaneous tissue of the abdomen was bile stained. The peritoneal cavity contained no fluid. The intestines were not distended. Most of the structures, such as the intestines, had a decidedly yellowish tinge. The liver showed some yellowish discoloration, especially of its right lobe. It extended 6 cm. below the right costal margin. The spleen was enlarged down to the umbilicus and several accessory spleens were present. The diaphragm was at the level of the third interspace on the right side and the fourth on the left.

Pleural Cavity.—Both cavities were patent throughout. A yellowish exudate was seen on the base of the left lung. The lungs were not crepitant throughout and showed rather large areas of a yellowish pink color. Some small irregular areas of pus were noted beneath the visceral pleura on the base of the left lung.

Pericardial Cavity.—The pericardial cavity contained about 20 c.c. of a clear, yellow fluid. The pericardial surfaces were smooth and tinged a yellowish color.

Heart.—The heart weighed 20 gm. The myocardium was pale and slightly decreased in consistency. The endocardium was smooth. Through the endocardium, at the site of the interventricular septum, was found an area that was dark and slightly wrinkled. This area was 1 cm. in diameter and apparently was the result of an infarct. There were two small petechial hemorrhages seen beneath the epicardium on the left auricle. The foramen ovale was closed. No congenital defects were noted. The valves were intact.

Lungs.—The right lung weighed 35 gm. and the left lung 30 gm. The middle lobe of the right lung was crepitant and yellowish pink. The upper and lower lobes were fairly firm and deep pink. The base of the left lung was congested. There were numerous patches of yellow exudate on the base of the left lung. Pus could be expressed from the cut surface of the left lower lung.

Spleen.—The spleen was enlarged and weighed 35 gm. It was dark purple and was firm. On cut section several light yellow fan-shaped areas were observed. The spleen extended down to a point on a level with the umbilicus. Two small accessory spleens were present, one being anterior and the other posterior.

Liver.—The liver weighed 145 gm. The left lobe was yellowish brown in color. The umbilical veins were patent. The capsule was smooth. It had a normal consistency and on cut surface presented many discolored areas. The gall bladder and bile ducts were patent. The gall bladder was filled with a cloudy yellow fluid.

Pancreas.—The pancreas showed no gross pathologic changes.

Gastrointestinal Tract.—The intestines were hyperemic, especially in the upper half. The stomach contained 25 c.c. of chocolate-colored material, with large amounts of stringy mucus. Several small hemorrhagic spots were demonstrated.

Adrenals.—The left adrenal weighed 5 gm. and the right, 3 gm. No gross pathologic changes could be detected.

Kidneys.—The right and left kidneys weighed 15 gm. each. They were markedly lobulated. The capsule stripped easily. The organs were quite pale. On cut surface, several fan-shaped uric acid crystal deposits were noted.

Genital Organs.—The genital organs were infantile and some clotted blood was noted on the end of the penis.

Brain.—The brain weighed 305 gm. The blood vessels were markedly congested. There were a few small tears in the tentorium. On cut section, a marked yellowish-black pigmentation of the thalamus and in the lateral walls of the third ventricle was noted. This also extended through the basal nuclei. The yellowish-black pigmentation was almost restricted to the nuclei and was most marked in the region of the olivary nuclei.

MICROSCOPIC FINDINGS

Heart.—The myofibrils were small and infantile. Occasionally the cross striations were visible. The interstitial capillaries were congested with red blood cells and nucleated cells. Small vacuoles could be seen within the cytoplasm of some of the myofibrils.

Lungs.—Many alveolar spaces were filled with neutrophils, fibrin, and large endothelial cells. These phagocytes were filled with pigment. The alveolar capillaries were engorged with leucocytes and red blood cells. The bronchioles contained an inflammatory exudate composed of neutrophils, red blood cells, and fibrin.

Spleen.—The capsule and trabeculae were thin. Only a few portions of Malpighian corpuscles were present. The pulp was congested with erythrocytes and nucleated red blood cells. Here and there occasional extramedullary hematopoietic centers were present.

Intestines.—Sections taken through the small intestines showed considerable autolysis of the mucosa. Several large areas of hemorrhage were present within the submucosa. Occasional dilated venules filled with nucleated red blood cells were present within the mucosa and submucosa.

TABLE I

LABORATORY DATA

	CASE 1		CASE 2	CASE 3				
Date	1/13/39	1/14/39	1/20/39	4/28/38	4/30/38	5/2/38	5/5/38	5/7/38
Hemoglobin	40%	48.2 %	36.4 %	27 %	56 %	45 %	53 %	52 %
Hemoglobin, grams	6.8	8.2	6.2					
Red blood cells	1,530,000	2,080,000	1,380,000	1,970,000	2,900,000	3,300,000	2,800,000	2,810,000
Color index	1.3	1.2	1.3	0.75			0.9	0.9
Volume packed red blood cells	24 c.c.	37 c.c.	20 c.c.					
Mean corpuscular volume	156.8 cu. μ	178.3 cu. μ	144.9 cu. μ					
Mean corpuscular hemoglobin	44.4 $\gamma\gamma$*	41 $\gamma\gamma$	44.9 $\gamma\gamma$					
Mean corp. hemo. concentration	28.3 %	22.1 %	31 %					
Nucleated red blood cells	71,500	55,000	25,500	many	many	few	few	few
Anisocytosis	marked	marked	marked	marked	marked	moderate	moderate	slight
Poikilocytosis	marked	marked	marked	marked	marked	moderate	moderate	slight
Polychromatophilia	marked	marked	marked	marked	marked	moderate	moderate	slight
Reticulocytes	25 %	30 %	8.5 %					
Leucocytes	15,000	19,000	24,000	62,500	16,000	8,500	6,000	8,500
Polymorphonuclear neutrophils	53	62	62	53	64	58	52	45
Polymorphonuclear eosinophils	2	2	1	0	5	3	0	3
Polymorphonuclear basophils	0	0	0	0	0	0	0	0
Monocytes	5	8	3	0	0	3	4	3
Small lymphocytes	35	26	32	44	32	35	44	47
Myelocytes	4	2	2	3	4	1	0	2
Myeloblasts	1	0	0	0	0	0	0	0
Platelets	350,000		200,000	243,800				
Bleeding time	4 min.		2 min.	5½ min.				
Coagulation time	3½ min.		2½ min.	5 min.				
Icterus index	300		200					
Initial hemolysis	0.40%		0.38 %	0.50 %				
Complete hemolysis	0.30%		0.32 %	0.30 %				
Wassermann reaction	negative		negative	negative				
Urinary urobilin	+		+					

*γ γ = micromicrograms.

Liver.—The liver cells were large and swollen. Some showed yellow granules within their cytoplasm. The Kupffer cells contained many black pigmented granules. The sinusoids were congested and numerous extramedullary hematopoietic centers were present within them.

Adrenals.—The reticulum showed a marked degree of cloudy swelling and postmortem degeneration. Within the medulla, small foci of hematopoiesis were present. Moderate congestion of the capillaries was noted.

Kidneys.—The Malpighian corpuscles were markedly congested. The convoluted tubules had undergone degeneration. Occasional extramedullary hematopoietic centers were noted in the cortex near the corticomedullary junction.

Brain.—The blood vessels of the brain were dilated and congested. The ganglion cells were dark and showed degenerative changes. Their cytoplasm, in some cases, appeared to contain yellow granules. The ependyma and meninges were intact. The leptomeninges presented some congestion of their blood vessels.

Thymus.—The capillaries within the medulla were congested. Hassall's corpuscles were intact. Occasional extramedullary hematopoietic centers were seen within the medulla.

CASE 3.—A white male was born on April 27, 1938, with a profound icterus. The obstetrician had reported that the amniotic fluid was golden yellow and, on removing the vernix caseosa with a sponge, noted it likewise had an intense yellow color. Delivery had been spontaneous.

The mother's pregnancy had been uneventful. Her Wassermann was negative. The family history was irrelevant.

Physical Examination.—Examination revealed a well-nourished and well-developed newborn male infant, who weighed 9 pounds. The skin was markedly jaundiced as were the sclerae. The liver and spleen were both tremendously enlarged, the latter extending to the iliac crest and to the midline of the abdomen.

A diagnosis of icterus gravis neonatorum was made, and, on April 29, 100 c.c. of whole blood was given by direct transfusion. The baby improved and was discharged from the hospital on May 7, 1938. Although the jaundice was still present, it was less intense than at birth. Further history of the case is lacking, with the exception of a report from the child's physician that at one year of age, the blood picture was quite normal.

It will be noted in the laboratory data, that the absolute number of nucleated erythrocytes was not computed, and this most probably accounts for the marked elevation of the total leucocyte count.

CONCLUSION

Three typical cases of icterus gravis neonatorum are presented with a review of the clinical, hematologic, and pathologic features of the disease.

We wish to acknowledge the assistance of Dr. John A. Lanford and Dr. H. J. Schattenberg, of the Department of Pathology, Tulane University, and Dr. Maurice Couret, pathologist at Hotel Dieu, New Orleans, for making pathologic studies on the cases presented, and to thank Dr. Roy E. de la Houssaye, Department of Pediatrics, Tulane University, for permission to report Case 3.

REFERENCES

1. Diamond, L. K., Blackfan, K. D., and Baty, J. M.: J. PEDIAT. 1: 269, 1932.
2. Lightwood, R., and Hawksley, J. C.: Proc. Roy. Soc. Med. 27: 255, 1934.
3. Hawksley, J. C., and Lightwood, R.: Quart. J. Med. 3: 155, 1934.
4. Rehn, H.: Jahrb. f. Kinderh. 75: 358, 1912.
5. Ylppö, A.: München, med. Wchnschr. 65: 98, 1918.

6. Idem: Ztschr. f. Kinderh. **17:** 334, 1918.
7. Josephs, H. W.: Medicine **15:** 307, 1936.
8. Wollstein, M.: Normal Blood in Infants and Children, Handbook of Hematology, Hal Downey, Editor, New York, 1938, Paul B. Hoeber, Inc., Vol. II, pp. 923-971.
9. Kato, K.: Folia haemat. **46:** 377, 1932.
10. Mackay, H. M. M.: Arch. Dis. Child. **8:** 221, 1933.
11. Hampson, A. C.: Lancet **1:** 429, 1929.
12. Stransky, E.: Ztschr. f. Kinderh. **51:** 239, 1931.
13. Pasachoff, H. D., and Wilson, L.: Am. J. Dis. Child. **49:** 411, 1935.
14. Darrow, R. R.: Arch. Path. **25:** 378, 1938.
15. Macklin, M. T., Lamont, J. A., and Macklin, C. C.: Am. J. Dis. Child. **57:** 349, 1939.
16. Rolleston, H. D.: Brit. M. J. **1:** 864, 1910.
17. Idem: Practitioner **104:** 1, 1920.
18. Parsons, L. G.: Acta paediat. **13:** 378, 1932.
19. Clifford, S. H., and Hertig, A. T.: New England J. Med. **207:** 105, 1932.
20. Andrews, H. S., and Miller, A. J.: Am. J. Dis. Child. **50:** 673, 1935.
21. Parsons, L. G., Hawksley, J. C., and Gittins, L.: Arch. Dis. Child. **8:** 159, 1933.
22. Parsons, L. G.: Lancet **2:** 1395, 1938.
23. Abt, A. F.: J. Pediat. **3:** 7, 1933.
24. Macklin, M. T.: Am. J. Dis. Child. **53:** 1245, 1937.
25. Schmorl, G.: Verhandl. d. deutsch. path. Gesellsch. **15:** 109, 1904.
26. Zimmerman, H. M., and Yannet, H.: Am. J. Dis. Child. **45:** 740, 1933.
27. Poynton, F. J., and Wyllie, W. G.: Arch. Dis. Child. **1:** 1, 1926.
28. Braid, F., and Ebbs, J. H.: Arch. Dis. Child. **12:** 389, 1937.
29. Wilson, S. A. K.: Rev. neurol. **20:** 229, 1912.
30. Sutherland, D. M.: Lancet **2:** 864, 1933.

A BACTERIOLOGIC STUDY OF 100 STILLBORN AND DEAD NEWBORN INFANTS

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THE purpose of this study was to demonstrate the presence and incidence of bacterial infection in the liver and spleen of stillborn babies and babies dying a few hours after delivery.

A review of the literature gives little information on such bacteriologic studies. In a treatise on autopsies of stillborn infants, Potter[1] states, "Bacterial infections, except syphilis, have a relatively unimportant role in the causation of either stillbirths or deaths during the first two weeks of life." Warwick[2] found bacteria in the lungs of only one of 19 stillborn infants in whom death was said to have been caused by pneumonia. In 1916, DeLee[3] reported four cases of stillbirth where cultural studies showed that systemic bacterial infection was the cause of death. Slemmons[4] recorded placental bacteriemia as a cause of death in 3 of 27 stillbirths.

METHOD

The livers and spleens of 80 stillborn infants and 20 babies who died within a few hours after delivery were used for this study. Of the stillborn group, 31 were slightly or moderately macerated. The autopsies were performed as soon as possible after delivery or death, the time interval varying from fifteen minutes to twenty-four hours. During the intervening period the bodies were kept in the morgue refrigerator.

The abdominal and thoracic cavities were opened, and the liver and spleen removed without injury. A face mask was worn and the hands were thoroughly cleansed with soap and water before culture materials were exposed. As large an area as possible of each organ was seared with a hot spatula and the openings made with sterile instruments. The superficial tissues were removed and pieces of the deeper tissue, approximately 1 cm. by 0.5 cm. by 0.5 cm., were rubbed on two blood agar plates and one liver infusion agar plate. These same tissues were each dropped into separate tubes of enriched beef heart broth with a pH of 7.6. One of the blood agar plates was incubated under anaerobic conditions using alkaline pyrogallol. The other blood agar plate and the inoculated liquid medium were incubated aerobically. The liver infusion agar plate was placed under 8 to 10 per cent carbon dioxide tension. The latter procedure was omitted after thirty-five cultures yielded no worthwhile results. All incubation was carried out at 37.5° C.

Macroscopic examinations were made after twenty-four hours. If no growth was seen, the cultures were left unopened. After forty-eight hours microscopic examinations were made using Gram's stain. Negative cultures were incubated 120 hours before they were discarded. After 50 cultures had been studied, it was decided that the liquid medium offered too many chances for contamination and the results were of doubtful value. Isolating such organisms as *Sarcina lutea* and *Micrococcus citreus* from an enriched broth medium without a corresponding result

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on solid medium would lead one to doubt the validity of positive enrichment results in all cases. Snyder[5, 6] and other workers discount their positive findings in enriched liquid medium.

In cultures where bacteria were found, subcultures were made, each strain isolated and identified when possible. The gram-negative bacilli were streaked on Endo's agar plates and the isolated colonies identified by carbohydrate fermentation tests. In cases where streptococci were found, enriched broth was inoculated with the suspicious colonies from the original cultures. When chains of gram-positive cocci grew, blood agar plates were streaked to observe typical colony growth.

RESULTS

Eight positive cultures were found in the group of 100 babies. In six of these, organisms were isolated from the liver only, and in the other two, from the spleen only. In none of the cases was the organism found concurrently in both liver and spleen. All of the infected babies were stillborn and macerated except one which survived delivery six hours (Table I).

TABLE I

SUMMARY OF CASES SHOWING BACTERIAL INFECTION

CASE	ORGANISM FOUND	ORGAN	CONDITION OF BABY	INTERVAL BETWEEN DEATH OR DELIVERY AND AUTOPSY
1	E. Coli	Spleen	Lived 6 hours	12 hours
2	E. Coli	Liver	Stillborn, macerated	10 hours
3	E. Coli	Liver	Stillborn, macerated	24 hours
4	E. Coli	Spleen	Stillborn, macerated	2 hours
5	E. Coli	Liver	Stillborn, macerated	3 hours
6	Str. gamma	Liver	Stillborn, macerated	7 hours
7	Anaerobic streptococcus (non-hemolytic)	Liver	Stillborn, macerated	9 hours
8	Unidentified species of the Genus Bacteroides	Liver	Stillborn, macerated	13 hours

Escherichia coli was isolated from 5 babies, the liver showing the organism in 3 cases and the spleen in 2. An anaerobic streptococcus, an unidentified species of the genus *Bacteroides*, and *Streptococcus gamma* (simplex) were cultured from the liver in the other 3 positive cases respectively. Seven of the 92 remaining cultures were contaminated, and 85 showed no growth.

REFERENCES

1. Potter, E. L.: Arch. Path. **25**: 609, 1938.
2. Warwick, Margaret: New York State J. Med. **37**: 2075, 1937.
3. DeLee, J. B.: J. A. M. A. **67**: 344, 1916.
4. Slemmons, J. M.: J. A. M. A. **65**: 1265, 1915.
5. Snyder, M. L.: J. PEDIAT. **9**: 637, 1936.
6. Snyder, M. L.: J. PEDIAT. **9**: 625, 1936.

50 ARMSTRONG STREET

THE POTENTIAL DANGERS OF TUBERCULIN TESTS

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NO AMOUNT of tuberculin injected into a noninfected individual will cause tubercle formation. In order to produce a tuberculous lesion it is necessary to inject tubercle bacilli. After an individual has been infected with tubercle bacilli a change occurs in the reaction of his tissues to the tubercle bacillus and its metabolic products. All tuberculin tests are based on this change in tissue reaction, known as the Koch phenomenon.

After tuberculous infection has occurred, the sensitized body tissues react in a specific manner to the injection of tuberculin. Besides the local reaction at the site of injection, there may be a perifocal inflammatory reaction surrounding an existing tuberculous lesion. This may result in progressive tuberculosis. It should be emphasized that the injection of tuberculin alone can only cause the activation of disease around an already existing tuberculous focus. The injection of tubercle bacilli is necessary to produce tuberculous lesions in new territory.

Experimentally it is easy to show a direct relationship between the amount of injected tuberculin and the resulting perifocal reaction around a tuberculous focus. The greater the amount of tuberculin injected, the more intense will be the ensuing perifocal reaction. The morphologic character of existing tuberculous lesions, however, and especially their content of living and dead tubercle bacilli determine the outcome of the perifocal reaction, which may be resolution or progression. Obviously the character and extent of the perifocal reaction vary both with the amount of tuberculin injected and with the character of the tuberculous focus. Caseous lesions, especially those without fibrous encapsulation, may show extensive perifocal reactions after tuberculin is injected. The perifocal inflammatory exudate may then undergo caseation and so cause progression of the lesion. The tissues surrounding a well-encapsulated or well-calcified lesion are less sensitive to tuberculin, and because of this fact a significant perifocal reaction may be absent even after the injection of large doses of tuberculin.

The morphology of a perifocal reaction around a tuberculous focus is essentially that of an exudative tuberculous tissue reaction. It is

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composed mainly of blood plasma, fibrin, red blood corpuscles, relatively few polymorphonuclear leucocytes, many lymphocytes, desquamated alveolar epithelial cells and blood histiocytes. The last two groups of cells are usually referred to as alveolar phagocytes. The histological character of a perifocal reaction, however, will vary from purely hemorrhagic perifocal zones to zones of leucocytic infiltrations with marked desquamation and proliferation of alveolar epithelial cells with lymphocytes and plasma. Or there may be merely an exudation of plasma with a little fibrin and a few lymphocytes.

History offers ample proof that the amount of tuberculin which gets into circulation and in contact with tuberculous lesions and the state of activity of the tuberculous foci in the body determine the character and extent of the tissue reactions to tuberculin injections. When Koch discovered tuberculin, he regarded it at first as a specific cure for tuberculosis. In the early attempts at therapy, large doses of tuberculin were injected subcutaneously. When this occurred in individuals with unstabilized tuberculous lesions, very severe perifocal reactions occurred. These "tuberculin pneumonias" progressed rapidly to caseation and excavation. Koch, himself, had a constitutional reaction and a reactivation of a fairly well stabilized pulmonary tuberculosis following the injection of several cubic centimeters of old tuberculin.

Twenty-five years ago it was common practice to attempt to diagnose tuberculosis of a joint by producing a focal reaction of redness, pain, and swelling with the subcutaneous injection of a solution of tuberculin. In the course of these injections it was not uncommon to observe areas of tuberculous pneumonia simultaneously with the local joint reaction. The pulmonary lesions were undoubtedly perifocal inflammatory reactions around unstabilized tuberculous pulmonary foci. Fortunately this method of establishing the tuberculous nature of a suspected lesion is no longer used.

Similar reactions may follow the liberation and absorption of tuberculotoxins from tuberculous lesions in the body. Recently we had the opportunity of seeing the picture of the diagnostic subcutaneous tuberculin test exactly reproduced in a case on the wards of the Children's Medical Service of Bellevue Hospital. A girl, 10 years old, who had chronic tuberculosis of the knee joint and cervical lymph nodes, with more recent pulmonary tuberculosis, developed a sharp rise of temperature with a marked increase in the swelling of the knee joint, which became red, hot, and tender. At the same time there was a marked increase in the number of moist râles heard over the tuberculous lesions. The whole picture subsided in forty-eight hours and was undoubtedly due to an autotuberculinization from a tuberculous lesion in her body.

We cannot control autotuberculinization, and it is obvious that the production of a focal reaction from this source is an undesirable but unavoidable accident. We no longer inject large amounts of tuberculin subcutaneously into individuals with unstabilized lesions in attempts at therapy or diagnosis. Are we sure that we always maintain a good control of tuberculinization by the intracutaneous test and that the Mantoux test is entirely harmless? It is possible that intracutaneous injection of such amounts of tuberculin as are generally used can produce focal reactions or harmful effects.

In children tuberculin tests are often done during the course of a fresh primary tuberculous infection when neither the primary focus nor its corresponding regional lymph nodes are well encapsulated. Moreover, in many children with unstabilized primary foci, dissemination of tubercle bacilli by the lymphohematogenous route has occurred, resulting in tubercle formation in other parts of the body. These newly created tuberculous lesions may remain unstabilized for a long time after the establishment of the primary tuberculous focus. Therefore, the injection of tuberculin into children, even in high dilutions, may produce results of clinical significance.

No definite proof has ever been advanced that the size or character of the local tuberculin reaction can be of help in determining either the location or morphology of the tuberculous lesions. In a recent study of 1,264 cases with measured reactions to Mantoux tests, Lincoln, Raia and Gilbert[1] again confirmed this fact. However, two factors were found which were definitely related to the size of the tuberculin reaction; namely, the age of the child and the amount of tuberculin injected.

In the series tested by Lincoln, Raia and Gilbert only 2.3 per cent of children of all ages had severe reactions to 0.01 mg., whereas 7.5 per cent had marked reactions when 0.1 mg. was used. Moreover, of the 1,264 children only 10 under 3 years of age showed severe local reactions and only 3 of these reacted to 0.01 mg. of tuberculin. Even when a tuberculin reaction becomes necrotic in an infant, it tends to remain small. In one of the 3 cases in infancy with marked reaction to 0.01 mg., the reaction at its height measured only 10 by 10 mm. However, we have morphologic evidence that intense focal reactions around existing tuberculous lesions may follow a Mantoux test even when there is no local evidence of a marked reaction to tuberculin.

CASE 1.—G. T., a white baby, 11 months old, was admitted to the hospital because he had been vomiting for a week. He was apathetic and drowsy, and his temperature ranged between 100 and 102° F. Examination revealed no other abnormalities. The fifth day after admission the baby had several localized convulsions of his right arm and left foot, each lasting about one-half hour. Spinal tap revealed a fluid with 45 lymphocytes to the cubic centimeter and with a sugar content of 40 mg. and protein of 60 mg. per cubic centimeter. The following day the spinal

fluid contained 250 cells, the sugar content had dropped to 23 mg. per cubic centimeter, and the protein rose to 88 mg. per cubic centimeter. The baby now showed the typical picture of tuberculous meningitis and died the following day. A Mantoux test with 0.01 mg. of tuberculin was given on the third day preceding death and was definitely positive. At 48 hours it showed redness and induration of 14 by 14 mm. but no vesiculation. Roentgenogram of the lungs (Fig. 1) was interpreted as showing primary tuberculosis of the right upper lobe with tuberculous involvement of the right bronchopulmonary and paratracheal lymph nodes and a hematogenous miliary tuberculosis of the lungs.

Postmortem Diagnosis.—Large progressive caseous and hemorrhagic primary tuberculous focus of the right upper lobe. Caseating tuberculous lymphangitis and lymphadenitis of the right bronchopulmonary, tracheobronchial and chain of paratracheal lymph nodes. Hematogenous miliary tuberculosis of lungs, liver, spleen and meninges. Caseous tuberculous meningitis.

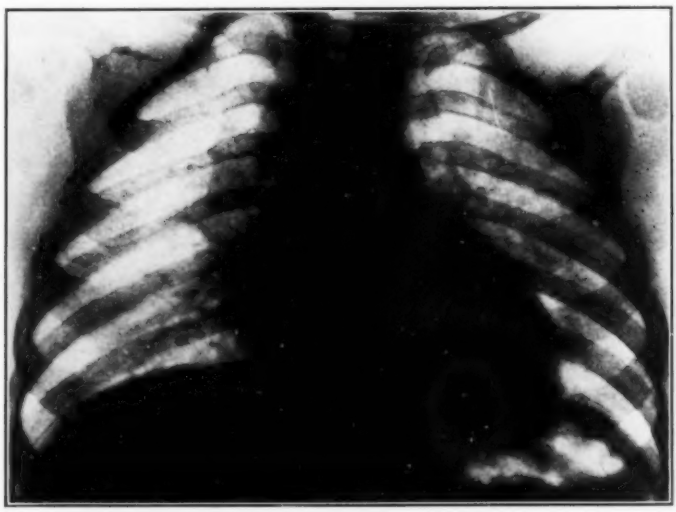

Fig. 1.—Case 1. Primary tuberculosis. Infiltration extending from hilum into right upper lobe. Enlargement of right mediastinum. Roentgenogram made day after tuberculin test and two days before death. Fine mottling throughout both lungs can be seen in original roentgenogram.

Microscopic Examination.—The primary tuberculous focus of the right upper lobe was not set off from the surrounding lung parenchyma by a sharp and distinct capsule formation of granulation tissue. It was encircled by a zone of tubercles which were densest near the hilum. The individual tubercles surrounding the primary focus as well as the central caseous parts of the focus were surrounded by zones of recent hemorrhage (Fig. 2). These hemorrhages also extended into the adjacent alveolar parenchyma, thereby giving the macroscopic impression that the primary focus itself was surrounded by a diffuse and irregular hemorrhagic zone. A group of conglomerate tubercles of the left upper lobe on microscopic examination also showed a perifocal hemorrhagic inflammatory reaction (Fig. 3).

It is obvious that the focal reaction after the tuberculin test did not alter the outcome of this case. The child was undoubtedly doomed by the meningitis before the tuberculin test was made. But if such a reaction can occur in an individual with

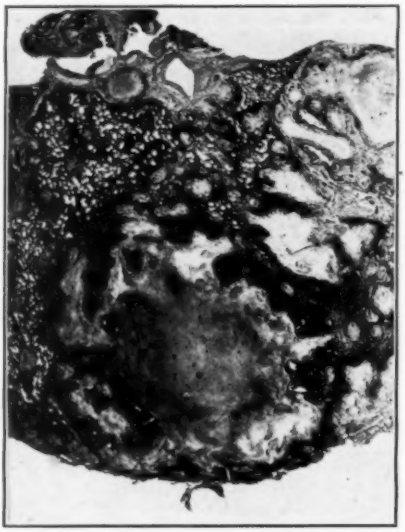

Fig. 2.—Case 1. Histologic section of primary focus of right upper lobe with caseous center and hemorrhagic perifocal infiltration. Caseating tuberculosis of lymphatics draining area of primary focus. The hemorrhagic reaction was probably produced by the Mantoux test.

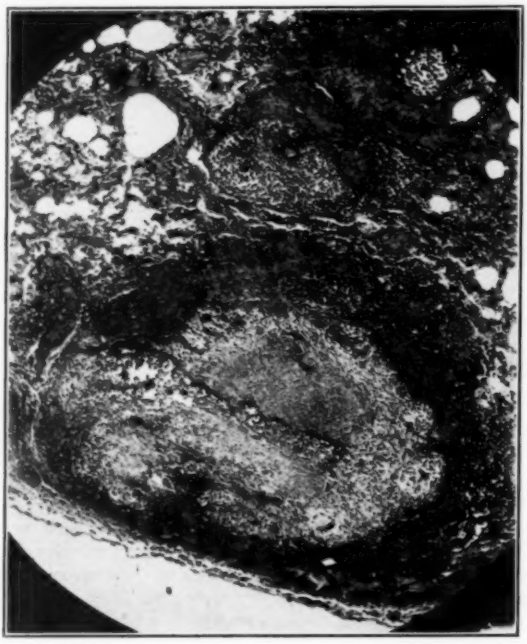

Fig. 3.—Case 1. Hemorrhagic perifocal reaction around tubercle in apex of left lung. Interpreted as part of general reaction to tuberculin test.

an unstabilized tuberculous lesion and give no local evidence of the severity of the lesion, what assurance have we that we are not causing perifocal reactions in other cases?

CASE 2.—T. S., a white infant, 6 months old, had been in contact with a tuberculous father for the first three months of life and at three months of age is said to have had a "bronchial cold." We later learned that a Mantoux test of 0.1 mg. was done in a tuberculosis contact clinic at this time and was positive. The child was well until the age of 6 months, when he was admitted to the Children's Medical Service of Bellevue Hospital with a generalized convulsion. He had a definite tonsillitis with enlarged and reddened tonsils with exudate in the crypts, a temperature of 102° F. and marked redness of both eardrums. Because of the convulsion, a lumbar tap was done and revealed a normal spinal fluid with sugar content of 81 mg. per cubic centimeter and protein of 33 mg. per cubic centimeter. A Mantoux test of 0.01 mg. was given as part of the routine examination since at the time we had no knowledge of his previous positive test. The tuberculin reaction measured only 12 by 12 mm. and was never vesiculated. The temperature gradually fell and remained normal for 24 hours, then rose to around 102° F. and remained at this

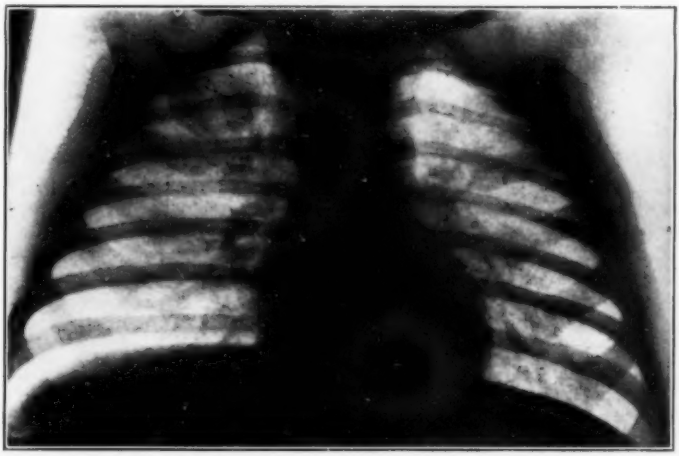

Fig. 4.—Case 2. Round and sharply defined infiltration of primary focus in right upper lobe. Enlargement of right mediastinal nodes. Roentgenogram made one week after Mantoux test and one week before death.

level for the following week. During this time the baby showed no abnormal neurological signs, and the eyegrounds were normal. A bilateral purulent otitis media was thought to account for the fever. A roentgenogram taken one week after admission (Fig. 4) was interpreted as showing primary tuberculosis of the right upper lobe with tuberculous involvement of the right tracheobronchial and paratracheal lymph nodes. Ten days after the initial convulsion the infant's temperature rose to 103° F., and he seemed acutely ill. There were no abnormal neurological signs, but it was noted that his spleen was easily palpable. Two days later slight internal strabismus of both eyes was noted, and a spinal tap at this time revealed spinal fluid with 127 cells per cubic centimeter, almost all lymphocytes, a sugar content of only 24 mg. per cubic centimeter, and protein of 40 mg. per cubic centimeter. The child died two days later, two weeks after the Mantoux test.

Post-Mortem Diagnosis.—Excavating and hemorrhagic caseous primary tuberculous focus of right upper lobe (Fig. 5) with extension into the surrounding pulmonary

parenchyma. Tuberculous lymphangitis with tubercle formation in the interfocal zone. Caseating tuberculous lymphangitis and lymphadenitis of the right bronchopulmonary, bronchial, tracheobronchial and chain of paratracheal lymph nodes. Acute generalized hematogenous miliary tuberculosis. Caseous tuberculous meningitis.

Microscopic Examination.—Lungs: Caseous primary tuberculous focus in the right upper lobe with hemorrhagic perifocal infiltration and extension into the surrounding pulmonary tissue. Predominantly productive miliary tuberculosis of both lungs. Spleen: Productive miliary tuberculosis. Liver: Miliary tuberculosis with hemorrhagic areas in the periphery of the caseous centers. Brain: Caseous tuberculous meningitis. Marked perifocal exudative infiltration around miliary tubercles in the fossae sylvii and the base of the brain.

Fig. 5.—Case 2. Caseous primary focus of right upper lobe corresponding to roentgenogram (Fig. 4). Hemorrhagic perifocal reaction probably due to Mantoux test. Similar hemorrhagic reactions were found around tubercles in the liver. Caseous tuberculosis of right bronchopulmonary lymph nodes.

This child had no evidence of meningitis when first admitted. He undoubtedly had a progressive primary tuberculous complex with invasion of the blood stream by lymphohematogenous extension resulting in the formation of a few isolated meningeal or cortical tubercles. It is probable that the injection of tuberculin may have caused a perifocal reaction around one or more of these unstabilized tubercles in the meninges or in the cortex, and that the perifocal exudate underwent caseation, thereby spreading the caseous process into the subarachnoid space with subsequent death of the child from meningitis. It has been our experience and also that of other observers,[2] that the majority of cases of tuberculous meningitis are due to a reaction around an older focus of tuberculosis in the cortex or meninges.

These two children (Cases 1 and 2), in spite of tuberculin reactions which were small and not vesiculated, showed evidence of hemorrhagic

focal reactions around their unstabilized tuberculous lesions which can only be interpreted as reactions to tuberculotoxins. We believe these morphologic changes were due to the Mantoux test. Without autopsy evidence, however, the possibility of a focal tuberculin reaction could not have been assumed.

Clinically, we occasionally see cases in which the onset of the child's illness can be attributed so definitely to the Mantoux test that it would be hard to deny the causal relationship.

CASE 3.—D. C., a colored girl, 9 years old, had been in good health until about Nov. 1, 1936. Then she had afternoon fever for several days and anorexia, and she began to lose weight and strength. A roentgen examination made on December 3 showed an infiltration of the right upper lobe with enlargement of the nodes at the right root (Fig. 6). The child was kept in bed at home, had excellent care, gained weight and strength and had no symptoms except an occasional rise of temperature to 101° F. Roentgen examination on January 14 showed a marked diminution in the parenchymal shadow with enlarged nodes still visible at the right hilum (Fig. 7). She was then in good condition and entirely symptom free; but, as the mother had decided that she could not continue her care at home, sanitarium treatment was discussed. In view of this, the physician thought it advisable to do a Mantoux test injecting 0.1 mg. of tuberculin on February 14. Within twenty-four hours the girl had a violent headache, a temperature of 103° F. and, in the twelve days before coming to the Children's Medical Service of Bellevue Hospital developed, in addition to loss of weight, progressive constipation and marked drowsiness. She had a typical tuberculous meningitis on admission with a spinal fluid sugar of 31 mg. per cubic centimeter and protein of 80 mg. per cubic centimeter. She became comatose and died 5 days after admission.

Here was a dramatic onset of meningitis immediately following the injection of tuberculin in a patient with a regressive but still unstabilized primary tuberculosis. In the mother's words, the tuberculin test "seemed to scatter the disease." It seems reasonable to postulate that, as in Cases 1 and 2, the injection of tuberculin caused an activation and rupture of a caseous meningeal or cortical tubercle into the subarachnoid space with subsequent meningitis.

During the postprimary stages of first infection tuberculosis we not infrequently see the development of neurological signs suggesting an early meningitis followed by complete subsidence of the signs. We believe such pictures are due to an exudative but not caseous perifocal reaction surrounding a tuberculous focus in the cortex or meninges. Such lesions like other exudative tuberculous lesions may resolve almost entirely leaving only a small amount of tuberculous granulation tissue. This interpretation is based on histological examination of the brains of several children who later died of other cause. In these cases fibrous adhesions were found at the base of the brain between the dura, the pia mater and the cortex. Microscopically the presence of epitheloid cells, lymphocytic infiltrations and areas of hyalinization of the granulation tissue confirmed the tuberculous nature of the healed

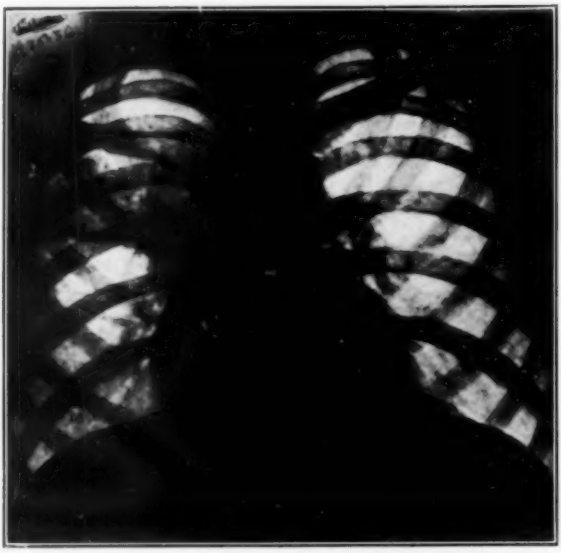

Fig. 6.—Case 3. Dec. 3, 1936. Infiltration of right upper lobe sharply defined by interlobar pleura. Marked enlargement of right mediastinal nodes.

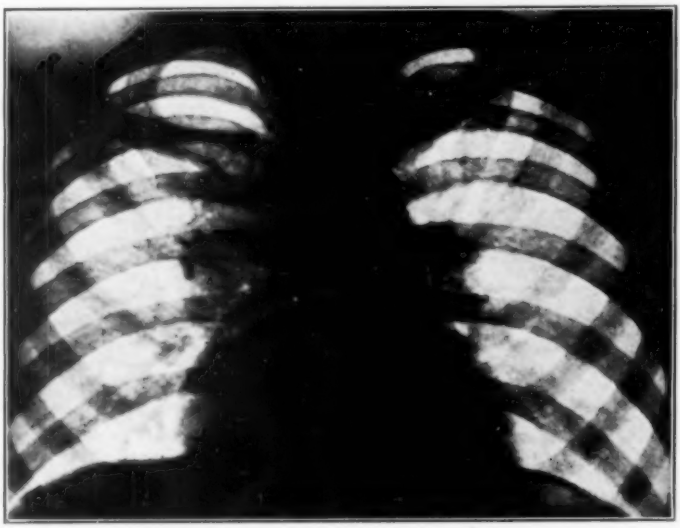

Fig. 7.—Case 3. Jan. 14, 1937. Resolution of right upper lobe lesion. Enlargement of right mediastinal lymph nodes. One month after this roentgenogram the patient was given a Mantoux test. Within twenty-four hours she became acutely ill and soon thereafter died of tuberculous meningitis.

lesion. The next case illustrates a perifocal exudate in the cortex or meninges which followed a tuberculin test.

CASE 4.—J. G., a white boy 6 years old, complained of fatigue and looked chronically ill, but had no fever nor abnormal physical signs. A Mantoux test with 0.1 mg. given in the dispensary produced a marked local reaction measuring 60 by 45 mm. with subsequent necrosis. He was admitted to the ward twenty-four hours after the test with a temperature which rose daily to 101° F. and on several occasions to 103° F. After one week he became afebrile and remained so for the following month. On admission the child was drowsy and apathetic, complained of headache, and had a positive Kernig sign. Spinal tap produced a clear fluid under markedly increased pressure, which was entirely normal in other respects. Roentgenogram of the chest revealed (a) parenchymal lesions (b) in the left lung with enlargement of the left bronchopulmonary nodes. There was no change in the pulmonary pathology during the boy's six weeks' stay on the ward. It may have been a coincidence that this episode followed immediately after the Mantoux test. The marked local reaction and the febrile episode which accompanied it lead us to believe that this was a focal reaction around meningeal tubercles such as we were able to demonstrate in Case 2. Fortunately in this case no caseous meningitis occurred.

We have seen perifocal reactions in the form of a sudden increase in the size of pulmonary parenchymal lesions, which were undoubtedly the result of an autotuberculinization, that is, of an endogenous dissemination of tubercle bacilli or tuberculotoxins. We have not seen these reactions following Mantoux tests, although undoubtedly they occur. We believe that our failure to observe focal reactions to the tuberculin test in the lung parenchyma is chiefly due to the fact that practically every child receives a Mantoux test before a roentgen examination is made, and consequently we see relatively few chest roentgenograms before and after tuberculin tests. In cases where the tuberculous lesion proclaims itself by symptoms and physical signs as in pleurisy with effusion, we have more evidence of a change in the pulmonary condition. Not infrequently cases of pleurisy with effusion are seen which we think can be attributed only to a tuberculin reaction, that is to a perifocal reaction around previously seeded pleural tubercles, usually of hematogenous origin.

CASE 5.—F. P., a 5-year-old Puerto Rican boy, in apparently good health, was given a Mantoux test with 0.1 mg. of tuberculin because of a history of contact with a case of tuberculosis one year before. The next day he developed fever, languor, and anorexia. Upon his return to the clinic four days later, a diagnosis of pleurisy with effusion was made by physical examination and roentgenogram. He had a markedly positive tuberculin reaction.

CASE 6.—G. R., a white boy, 10 years old, whose mother had tuberculosis, was admitted to the Children's Medical Service of Bellevue Hospital because of a mild attack of chorea. A double Mantoux test of 0.01 and 0.05 mg. was given on admission and the reaction to the 0.01 measured 10 by 10 mm. after forty-eight hours. At the same time the area around the test with 0.05 mg. was 30 by 30 mm., and this later became necrotic. Roentgenogram the day after admission (Fig. 8) showed essentially negative lung fields. Four days later he had the physical signs and roentgen picture of a pleural effusion extending to the second left interspace (Fig. 9).

Thoracentesis revealed a yellow, slightly cloudy fluid with 1200 cells to the cubic centimeter, practically all lymphocytes. The white blood count at this time was 8,500 with 50 per cent polymorphonuclear leucocytes. The pleural fluid diminished slowly, and he was transferred to a tuberculosis sanatorium five months later.

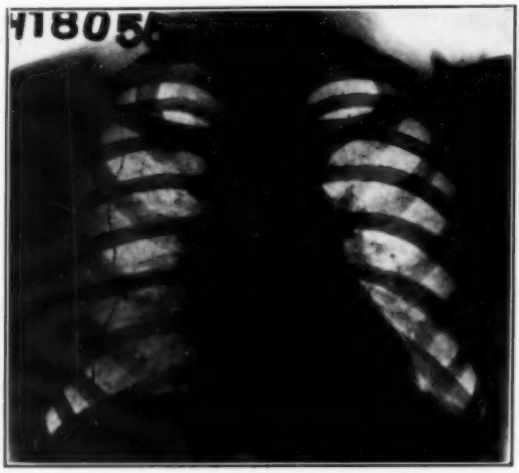

Fig. 8.—Case 6. July 1, 1937. Essentially negative lung fields on admission. Child admitted because of chorea. Mantoux test given on date of this roentgenogram.

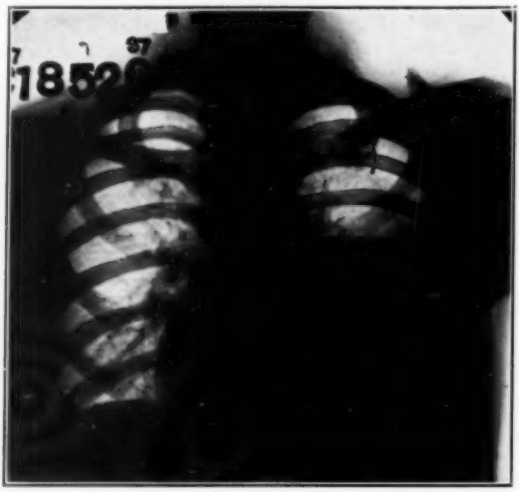

Fig. 9.—Case 6. Physical signs of pleural effusion at left base appeared four days after Mantoux test. Fluid obtained by thoracentesis was typical of tuberculous effusion.

In Cases 5 and 6 the pleural effusion followed the tuberculin reaction so quickly that it seems reasonable to interpret the pleurisy as the result of an exudative perifocal response to the Mantoux test.

Occasionally we see other manifestations of focal response to Mantoux tests. We have seen a previously palpable cervical node become enlarged and tender and the overlying skin reddened and hot. This occurred simultaneously with the development of pleurisy with effusion and followed closely on a Mantoux test with a severe local reaction. We have observed a subsiding phlyctenular conjunctivitis become markedly inflamed subsequent to a Mantoux test. It is not unusual to discover one or more phlyctenules, in previously normal eyes, within twenty-four hours of a Mantoux test. The skin may also show focal tuberculin reactions. One 8-year-old girl who had a marked local reaction to 0.01 mg. of tuberculin within ten hours after the test had a sharp rise of temperature to 103° F., which persisted for forty-eight hours, and during this febrile period she developed a typical

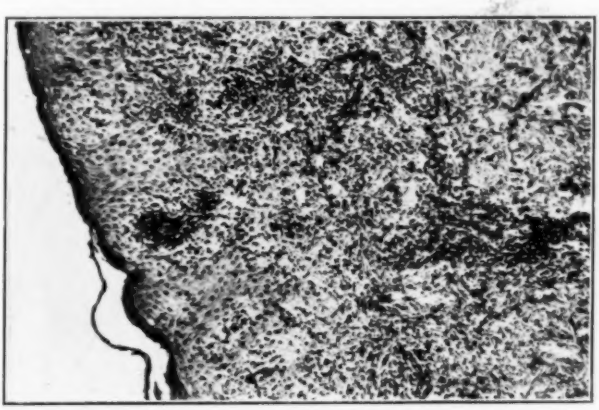

Fig. 10.—Microscopic section of biopsy of papular lesion of left forearm showing focal hemorrhages, epitheloid cells and lymphocytic infiltrations. Lesion characteristic of an early tuberculide. This papule was part of an eruption occurring four days after a tuberculin test.

case of erythema nodosum. A white boy, 10 years old, was given a tuberculin test with 0.05 mg. and four days later the patient reported that "spots" had appeared around the tuberculin reaction, which was not vesiculated, and not very large. He reported that these subsequently had spread over his body. When he was seen a week after the Mantoux test, a moderate number of papules with depressed centers was grouped around the area of the tuberculin reaction and a lesser number over his legs and other forearm with a few on the trunk. Biopsy of one of these areas showed an inflammatory lesion filled with epithelioid cells, focal hemorrhages, and lymphoid cell infiltration. The picture was very suggestive of an early tuberculide (Fig. 10). The last two cases were isolated ones, and it will be noted that they occurred in older children. Any of these reactions could, of course, have

conceivably been due to autotuberculinization, but their occurrence after Mantoux tests would seem to be more than coincidence.

We are presenting the next case in order to emphasize again that it is particularly in the recent and in the unstabilized tuberculous lesions that we must beware of the potential dangers of the Mantoux test. A well-stabilized lesion, even an extensive one, is much less likely to react unfavorably to a tuberculin test than an unstabilized lesion, although the latter may be small in extent.

CASE 7.—T. G., a colored girl aged 9 years, had a prolonged exposure to tuberculosis in infancy. When she was admitted to the Children's Medical Service, this contact history was not known; she therefore received the double dose of 0.01 and 0.05 mg. of tuberculin which was for a time routinely given to patients not suspected

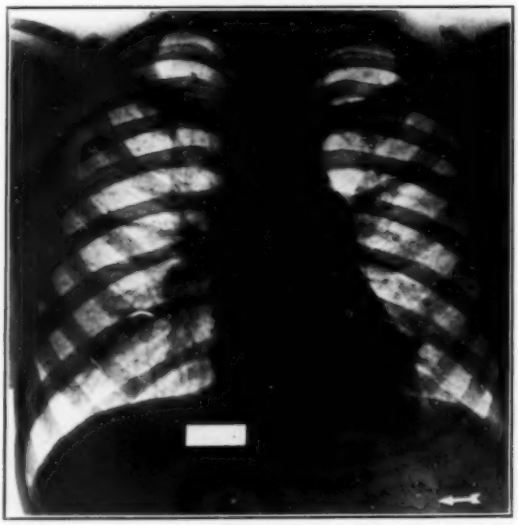

Fig. 11.—Case 7. Large calcified primary complex. Calcified hematogenous foci in both apices. Following a Mantoux test with a large dose of tuberculin, this child had a severe local reaction with fever. No focal reaction could be demonstrated probably because the lesions were well stabilized.

of tuberculosis. The following day by an error she was given 0.2 mg. intracutaneously which would normally have been given only if after five days she was found to be negative to the first tests. She received therefore about 0.25 mg. of tuberculin within twenty-four hours. The day after the second test her temperature rose abruptly to 102° F. and remained elevated for four days. The Mantoux test with 0.01 mg. did not vesiculate, but both the tests with 0.05 and with 0.2 mg. became vesiculated, ulcerated, and painful, requiring dressings for several weeks. Aside from the local reactions and the fever, careful examinations including repeated roentgenograms gave no suggestion of any focal reaction, although this child gave evidence of having had a progressive primary tuberculosis. Roentgenograms (Fig. 11) showed a large calcified primary focus with calcification in the bronchopulmonary and mediastinal nodes and calcifications of hematogenous foci in both apices and in the spleen. In addition she had calcifications in the cervical and retroperitoneal

lymph nodes. Failure to show a perifocal reaction around any of these lesions following a general reaction to the injection of tuberculin was probably due to the stability of the tuberculous lesions.

SUMMARY AND DISCUSSION

It is evident that constitutional reactions may follow Mantoux tests. In the series studied by Lincoln, Raia, and Gilbert at Bellevue Hospital, they were much more common over the age of 4 years and more common when 0.1 mg. was given than with a test of 0.01 mg.

It is also evident that focal reactions may occur around existing tuberculous foci. It has been difficult to demonstrate these in the lung by means of the roentgen ray, possibly because the Mantoux test in practice usually precedes the roentgenogram. However, focal reactions in the pleura and meninges, in the superficial lymph nodes, the sclerae, and the skin have been observed.

Local severe tuberculin reactions leading to vesiculation or necrosis are more frequently seen in the groups 5 years of age and older than in infants and occur much more frequently with 0.1 mg. than when 0.01 mg. is given. In the older groups severe local reactions are almost invariably present when there is a focal or constitutional reaction. In infancy general or focal reactions may be seen when the local reaction is not necrotic and occasionally when it is vesiculated or necrotic but small.

Tuberculin is safer to use in well-stabilized, even though extensive lesions, than in progressive or active lesions, however small.

Since at least 75 per cent of ambulant cases infected with tuberculosis will respond to the initial dose of 0.01 mg. and the risk of severe reactions is so much less with this dosage than with larger amounts, it would seem logical to urge the general adoption of this dose as the maximum initial test. Moreover, since it has been shown that patients who have had progressive primary tuberculosis only rarely develop negative tuberculin reactions during childhood, it would seem reasonable not to repeat tuberculin tests which have been positive, since further testing is of no conceivable use in the care of the child. If it could be made feasible, some method should be devised whereby a child who has had a positive Mantoux test could be branded in some way to preclude further testing at least until his disease had healed. Moreover, we should go even further and suggest that when tuberculosis is suspected because of a history of contact with a case, or for any other reason, roentgenography, or at least fluoroscopy, might well precede a Mantoux test.

The tuberculin test is so simple to do that it has become popular as a routine measure. Many hospitals perform routine Mantoux tests on all patients admitted; some convalescent homes require the tests before accepting a child; practically all tuberculosis sanitaria repeat

tests on children admitted with the history of previous positive tests. Most case-finding projects make no attempt to find out whether previous tests have been made. Many tuberculosis clinics and chest clinics on pediatric services repeat tests that have been reported as positive. We have seen children who have had as many as 10 positive Mantoux tests within less than two years.

We wish in no way to detract from the great value of tuberculin as a help in case finding and in differential diagnosis, but a Mantoux test should be regarded as a help in diagnosis, not essential when the diagnosis has been definitely established. And above all it is important to remember that when a Mantoux test is done, material is injected which is potentially dangerous and able to create an undesirable reaction around unstabilized tuberculous foci.

REFERENCES

1. Lincoln, E. M., Raia, A., Gilbert, L. A.: J. PEDIAT. 12: 479, 1938.
2. Rich, A. R., and McCordock, H. A.: Bull. Johns Hopkins Hosp. 52: 5, 1933

THE CLIMATIC FACTOR IN PRECIPITATING ACUTE TONSILLITIS IN CHILDREN

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THE climatic factor, as expressed in terms of the weather and the season, in recent years has begun to receive the careful attention of a considerable number of European and American investigators. Apart from that of Magelssen,[1] whose pioneering determination has survived the unpopularity of his thesis these many years, few persistent efforts have been devoted to the association of meteorology and disease during the last three decades. In this country Huntington[2] and Mills[3] have done much to create an understanding of the relation of climate to health, but Petersen[4] in particular has described the day-by-day weather influences on the normal person and on the patient. In Europe the gradual return of interest in meteoropathology is due primarily to the wide circulation of deRudder's[5] monograph in 1931. Since that time there has been published a whole series of papers dealing with the role of the meteorologic environment in surgical conditions, obstetrics, otolaryngology, ophthalmology, gynecology, and urology.

In the field of contemporary otolaryngological studies, Gover[6] and his associates have described the distribution of common colds and the relation to corresponding weather conditions, Montgomery[7] has reviewed the effect of climate on diseases of the upper respiratory tract, and Randall[8] has studied the association of meteorologic turbulence and the opportunity for sinus infection. Greifenstein[9] found a distinct association of postoperative angina and change of the seasons. Gregorini[10] has studied the association of peritonsillar abscess and the relation to weather, and Wirth and Laucheimer[11] have observed the association of weather (the passage of atmospheric fronts) and acute infections of the upper respiratory tract.

The fact that the weather and the season can be measured with considerable accuracy constitutes a distinct advantage. Definite alterations such as those involved in daily temperature changes are measurable, as are likewise barometric pressure, daily average wind velocity, daily sunshine scale, and daily precipitation. A comprehensive meteorogram, a graphic method used to show the passage of the air masses, would incorporate these climatic ingredients.

Sargent[12] recently investigated the common cold in normal young men observed under normal conditions of activity and all subject to

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the same meteorologic conditions. When an individual was observed from day to day, the initiation of a "sore throat" or "cold" was always preceded by an episode involving a fall in daily temperature. In regions where there is greater environmental variability, there will be greater variability of the vessels of the mucous membranes; consequently there will be greater opportunity for penetration of the flora of the upper respiratory tract.

For purposes of clarification it must be kept in mind that the human organism must adjust itself periodically to two wholly different types of atmosphere. A sudden fall in air temperature is usually associated with the passage of a polar air mass (cold front or polar front). This brings with it not only a change in temperature but lessened humidity and increase in barometric pressure. On the other hand, increasing temperatures are characterized not only by a warmer air mass (warm front or tropical front) but also by greater moisture content and lower barometric pressure with the warmer air.

The precipitation of disease takes place in the wake of a cold front. At this time there is a change in the functional status of the mucous membranes of the nose and throat. A latent period or "lag" of a few hours to one or more days may occur before the actual initiation of the clinical symptoms. Although one cold front may be passed without incurring harm, it is often the superimposed cold front that results in further damage. A second insult, striking the individual before adequate recovery has been possible, may contribute to further biologic instability. The infall of cold air is pathogenetic, either directly because of the meteorologically induced vascular spasm or indirectly because of changes following in the wake of the vascular spasm.

What is the biologic significance of the cold front? Primarily and of greatest importance, it indicates that the organism has responded to the environmental situation with a sympathicotonia of such degree that an unusual vasomotor reaction has been apparent in the nasal or pharyngeal mucous membrane, the amplitude of the upset becoming evident to the subject because of the reflex nerve effect (sneezing or tickling), because of mucous membrane contraction or swelling with unusually marked secretion of either thin or mucoid secretion. All of these phenomena may be evanescent, may last a relatively short time, and then disappear wholly, or these vasomotor phenomena, whether obvious to the subject or not, may be followed by the penetration of a resident flora, with either a relative transient or a more prolonged inflammatory reaction of the surface.

The beginning is always a pressor episode, that is, a period during which time there is a relative anoxia of the tissues. It may occur in midsummer with the skin vessels normally dilated and the skin itself covered with a film of sweat, when a seemingly minor change in the

speed of surface evaporation, or an apparently minor change in the environmental temperature, may cause sudden and widespread contraction of the peripheral vascular bed. It may occur in the tropics or in the semitropics where the chill of the "night air" notoriously may initiate a similar effect. It may follow in the winter when habituation of the skin vessels is already well established; but at this time a seemingly minor environmental change may bring about a relatively negligible mucous membrane alteration, of sufficient magnitude, however, to permit the more ready passage of organisms. These organisms resident on the mucous membrane during the winter and spring are of a different kind as compared with those present in the summer and autumn.

As long as oxygen adequacy is maintained, resistance is good. The moment oxygen inadequacy occurs, resistance is impaired. Many years ago Pawlinoff[15] stressed the point, and recently Locke[13] has referred to the significance of frequent changes in environmental temperature as associated with lessening of resistance and has demonstrated the dependence of the mechanisms of resistance on oxygen adequacy both in human beings and in experimental animals.

Among the meteorological changes, the effect of cold is only one of the factors that precipitate change. Thus, the lack of sunshine, the change in barometric pressure, exposure to precipitation at the interface of the air masses, the change in humidity, and increased wind velocity, to mention but a few, are all of importance, and the individual's response to an environmental change, whether he be outdoors, in his home, or in a hospital, is exceedingly complex. The vasomotor effects occur simultaneously in the population at large, which is subjected to the passage of the air mass, although it should be understood that the reaction will differ in amplitude and occasionally in the phase direction, and that at times there may be an accentuation or delay in the reaction of the organism to the environmental change in different kinds of people.

Petersen has described in detail the vasomotor and biochemical changes that are induced in the population when a polar air mass passes over the group. At first the capillaries are less permeable, the blood pressure is increased, the tissues are less hydrated, and the blood is relatively more alkaline (CO_2 content decreased, blood pH increased). In general, this might be called a period of sympathicotonia which finds its reflection in the peripheral tissues, including the mucous membranes of the nose and throat. Gradually the vascular spasm is dissipated, the vessels become dilated to accommodate the increased demand of the organism for greater oxygen consumption, the blood pressure falls, the membranes become more permeable, and the tissues become relatively more acid and hydrated. At this time,

presumably, the opportunity for bacterial penetration is greater. The investigations of Burrows[14] have been of particular significance in this connection.

Later, after the bacteria have penetrated into the mucous membranes, disease develops either by local reactivity of the tissues, dissemination from the zone of penetration, or localization in the body after dissemination. Localization in the tissues will be favored immediately in association with the alteration induced by vascular spasm.

Thus, the shift from one type of atmospheric mixture in which the population is existing to one diametrically opposite in most of its qualities is definitely associated with a shift in the physiologic phase, and, under normal conditions, the population is constantly swinging from a phase where vascular spasm is enhanced to one where vascular dilatation is augmented, and vice versa. The condition is one of continuous flux in practically every physiologic and biochemical balance. In the human being we deal with a continuous rhythm of increasing and decreasing resistance from hour to hour, from day to day, and from season to season; and environmental alterations (cooling, for instance) that can be useful to one individual by increasing tone during the phase of vascular spasm may, in the inadequate individual, lessen resistance because of increasing fatigue.

CLINICAL OBSERVATIONS

Nineteen cases of acute tonsillitis in children ranging in age from one year to ten years, involving both sexes, each child sufficiently ill to warrant hospitalization in a pediatric hospital during 1938, are presented to illustrate the significance of the onset of the cold front in precipitating the disease. Although scores of patients with acute tonsillitis were seen, only 19 were regarded as sufficiently ill to require hospitalization. Simplified forms of meteorograms have been prepared from the United States meteorologic data supplied by the local weather bureau. A comprehensive meteorogram would include the daily temperature, barometric pressure, daily average wind velocity, daily sunshine scale, and daily precipitation. For purposes of simplification, the high and low range of the daily temperature can be regarded as an adequate index of meteorologic change.

CASE REPORTS

CASE 1.—B. A., age 1½ years, female, developed an acute tonsillitis and a bilateral otitis media following a clinical course which began with convulsions Jan. 7, 1938 (Fig. 1, *1*). The meteorogram establishes a definite polar front striking the city at this time.

CASE 2.—During this same cold front, M. P., a 6½-year-old female, also developed an acute follicular tonsillitis associated with mumps. The first clinical manifestation was a convulsion. The crest of the cold wave had just passed, and Jan. 10, 1938 (Fig. 1, *2*), the symptoms began to develop.

CASE 3.—On Jan. 30, 1938 (Fig. 1, *3*), a rapidly falling temperature was sufficient to precipitate an acute membranous tonsillitis in D. B., a 3-year-old male. The time periods involving the first three cases incorporated polar fronts which contained the coldest temperatures during the first ten months of 1938.

CASE 4.—A series of polar air masses had passed over the city, and with the barometric crest of Feb. 28, an acute follicular tonsillitis in a 1½-year-old female, V. B., was precipitated (Fig. 2, *4*).

CASE 5.—On April 15, 1938 (Fig. 3, *5*), R. M., a 4½-year-old male, first had fever in a clinical course which immediately evolved into acute follicular tonsillitis and inguinal adenitis. It will be observed that April 15 represents the sudden passage of a cold air mass.

CASE 6.—The next cold wave on April 20, 1938 (Fig. 4, *6*), precipitated an acute follicular tonsillitis in G. H., a 10-year-old boy, whose initial symptoms were abdominal pain and vomiting.

CASE 7.—During the month of May, 1938, five children were sufficiently ill with acute throat infections to warrant hospitalization. Of this group, M. B., a 2-year-old female, developed acute tonsillitis following the onset of the initial symptoms, high temperature, vomiting, and difficulty in breathing on May 1, 1938, a day of minimal temperature (Fig. 4, *7*).

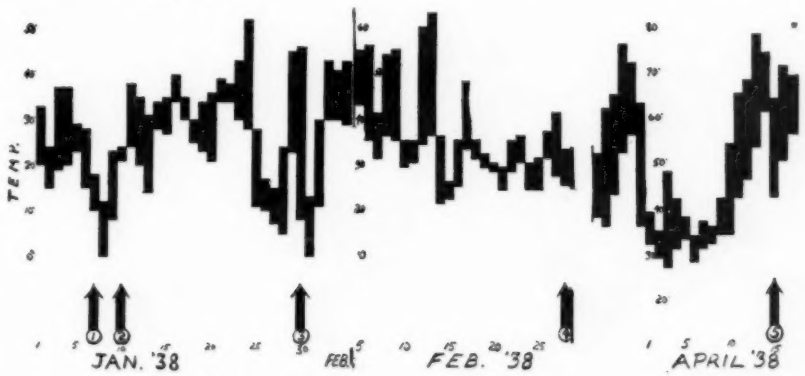

Fig. 1. Fig. 2. Fig. 3.

CASE 8.—Following a tropical front, the advent of a well-marked polar front episode was sufficient to precipitate an acute follicular tonsillitis in J. H., a 3-year-old female. The initial symptoms, high fever, vomiting, and abdominal pain appeared on May 6, 1938 (Fig. 4, *8*).

CASE 9.—On May 12, 1938 (Fig. 4, *9*), R. G., a female, developed an acute tonsillitis resembling a scarlet throat while she was in the hospital with a hip ailment. It will be noted that May 13 was the coldest day of the month.

CASE 10.—On the next day which is part of the same polar episode, May 13, 1938 (Fig. 4, *10*), G. T., a 7-year-old female, complained of sore throat and fever, symptoms that were realized in an acute septic tonsillitis with hemorrhage from the mouth.

CASE 11.—R. S., a 5-year-old boy, developed an acute septic tonsillitis, the initial symptoms consisting of sore throat, vomiting, fever, and abdominal pain, first appearing on May 22, 1938 (Fig. 4, *11*). This day marks the bottom of the cold wave.

CASE 12.—D. B., a 7-year-old female, had a "head cold" for two weeks, the onset coinciding with a barometric crest. On July 5, 1938 (Fig. 5, *12*), the passing of a minor polar front was sufficient to precipitate headache, sore throat, and a temperature of 102° F., the prodromal onset of an acute follicular tonsillitis.

CASE 13.—On the following day another child, E. P., a female, was irritable and ran a high fever, the onset of an acute follicular tonsillitis (Fig. 5, *13*). As in the case of the preceding child, this patient also had complained of cough and a "head cold" for a period of three weeks, thus dating back to the preceding barometric crest.

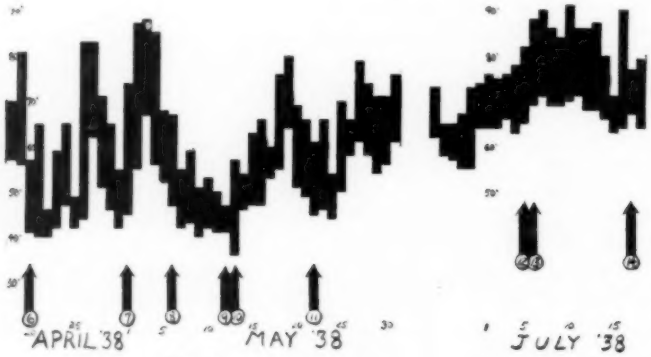

Fig. 4.

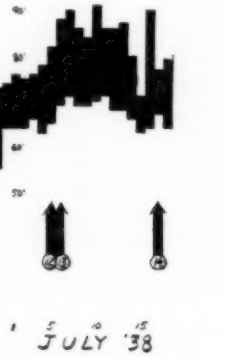

Fig. 5.

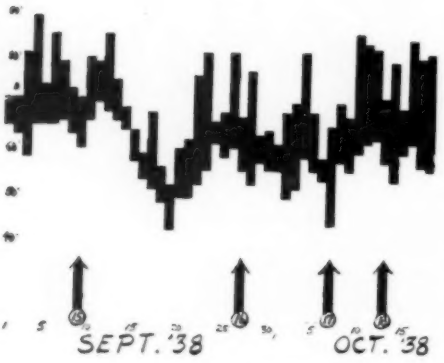

Fig. 6.

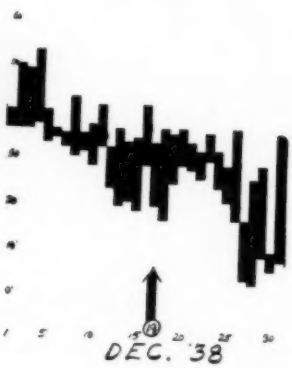

Fig. 7.

CASE 14.—A minor polar front episode was sufficient to precipitate the prodromal symptomatology, a temperature of 102° F. and anorexia, of an acute follicular tonsillitis in a 1-year-old infant female, P. K., on July 17, 1938 (Fig. 5, *14*).

CASE 15.—With the severe meteorologic disturbance (heavy precipitation and a fall in temperature) on Sept. 9, 1938 (Fig. 6, *15*), a 2-year-old male, J. M., suddenly vomited, had a sore throat, and had a fever of 103° F. These symptoms were followed shortly by an acute follicular tonsillitis and a cervical adenitis.

CASE 16.—C. C., a 1½-year-old male child, developed acute tonsillitis, bilateral otitis media, and left lower lobe pneumonia following a nasal "cold" which had its onset on Sept. 27, 1938 (Fig. 6, *16*), the date of a well-demonstrated polar front.

This child was admitted to the hospital at the time of another polar episode on Oct. 6, 1938.

CASE 17.—On Oct. 7, 1938 (Fig. 6, *17*), D. M., a 2-year-old male, became restless and slept very poorly. These prodromal signs proved the onset of an acute follicular tonsillitis.

CASE 18.—An acute follicular tonsillitis and bilateral otitis media had their onset on Oct. 13, 1938 (Fig. 6, *18*), in R. C., a 1-year-old female infant, when the child refused to eat and held her hand over the left ear. A polar front had passed a few hours previously.

CASE 19.—L. L., a male, developed acute tonsillitis, otitis media, and bronchopneumonia following a polar front on Dec. 17, 1938 (Fig. 7, *19*), when he began to cough and had a "head cold."

SUMMARY

The precipitation of acute tonsillitis in children most often takes place in the wake of a "cold front," a time when the air temperature falls, the barometric pressure increases, and there is lessened humidity. At this time there is a change in the functional status of the mucous membranes of the nose and throat. A latent period or "lag" of a few hours to one or more days may occur before the actual initiation of the clinical symptoms.

Nineteen cases of acute tonsillitis in children, each child sufficiently ill to warrant hospitalization, are presented to illustrate the significance of the onset of the "cold front" in precipitating the disease.

REFERENCES

1. Magelssen, A.: Wetter und Krankheit, Specieller Theill, Christiana, Johansen, 1894.
2. Huntington, E.: Civilization and Climate, New Haven, 1933, Yale University Press.
3. Mills, C. A.: Living With the Weather, Caxton Press.
4. Petersen, Wm. F.: The Patient and the Weather, Vols. I-V, Ann Arbor, 1934-1938, Edwards Brothers.
5. deRudder, B.: Wetter und Jahreszeit als Krankheitsfaktoren, Berlin, 1931, Julius Springer.
6. Gover, M., Reed, L. J., and Collins, S. D.: Pub. Health Rep. **49**: 811, 1934.
7. Montgomery, R. R.: Ann. Otol., Rhin. & Laryng. **45**: 704, 1936.
8. Randall, G. M.: Med. Rec. **144**: 370, 1936.
9. Greifenstein, A.: Arch. f. Ohren-, Nasen- u. Kehlkopfh. **142**: 68, 1936.
10. Gregorini, F. V.: Osp. maggiore **23**: 449, 1935.
11. Wirth, E., and Laucheimer: Acta oto-laryng. **19**: 304, 1935.
12. Sargent, F.: Studies in the Meteorology of Upper Respiratory Infections, Bull. Am. Meteorol. Soc. **19**: 385, 1938.
13. Locke, A.: J. Infect. Dis. **60**: 106, 1937.
14. Burrows, H.: Some Factors in the Localization of Disease, London, 1932, Baillière, Tindall and Cox.
15. Pawlinoff, C.: Das Sauerstoffmangel, Berlin, 1902, A. Hirschwold.

185 N. WABASH AVENUE

RESPIRATORY INFECTIONS: INCIDENCE AND CLINICAL COURSE AS OBSERVED IN A FLORIDA PEDIATRICS PRACTICE

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THE occurrence and intensity of disease during childhood is influenced by factors other than the immunologic response of the individual. Intimacy of exposure, climate, environment, and the virulence of the offending organism constitute some of these factors. A knowledge of the incidence and certain features characteristic of the clinical course of respiratory infections in south Florida is important to physicians throughout the United States. The seasonal change in population presents problems peculiar to this resort center. Effects upon the community health should interest medical men in other sections of the country, since many of their patients spend a portion of their winters in Florida.

It is impossible to differentiate accurately the course of infection among native or resident Floridians from that among tourists or temporary residents, because records of cases do not include this information. Clinical observation emphasizes the fact that the incidence of colds among natives is definitely higher during the winter season coincident with the peak of tourist population.

The fact that many children are brought to Florida during the winter to convalesce from respiratory infections acquired elsewhere may explain the high incidence of colds among local children during this season. It has been noted by Kneeland and Dawes[1] that the respiratory tracts of newborn infants are sterile but soon show the flora of normal adults in their environment. The type of contact encountered by older children in schools or other public places might by analogy be assumed to determine the bacterial seeding process in their upper respiratory tracts.

Spiesman and Arnold,[2] in 1937, reported a clinical and experimental study of host susceptibility to common colds. They have observed a definite relationship between the vasomotor reaction of the respiratory mucosa to thermal stimuli and individual resistance to infections involving the respiratory tract. Taylor and Dyrenforth[3] have noted a predisposition toward colds as an immediate result of chilling of the body surface. So long as one can maintain a normal temperature, immunity is not necessarily reduced, regardless of environmental changes. It must be remembered that the homes and apartments in south Florida are not generally equipped with central heating plants and that occasionally sudden changes of weather occur.

The present study was undertaken in an effort to determine how often and what type of respiratory infection is observed in a representative Florida pediatric practice. It includes an analysis of approximately 2,000 chart records and represents a comparison of 1,020 hospital cases with a similar group of private patients encountered in office or home practice. A consideration of this relatively large number of different individuals effectively eliminates seasonal variation and short epidemics of respiratory infection. The figures represent the number of children in whom each disease has occurred. Thus, the confusing factor of recurrent respiratory infections in the same individual was avoided.

Tables I and II indicate the incidence of respiratory infections among the patients considered, subdivided into diseases of the upper and of the lower tract and classified according to age groups.

TABLE I

INCIDENCE RESPIRATORY INFECTIONS AMONG 1,023 HOSPITAL PATIENTS*

TYPE	UNDER 1 YR.	1-3 YR.	3-5 YR.	5-7 YR.	7-9 YR.	9-12 YR.	TOTAL
Upper	38	68	46	39	25	29	245
Lower	27	60	31	15	16	11	160
Total respiratory infections among 1,023 records							405 (39%)

*Jackson Memorial Hospital, Miami, Fla.

TABLE II

INCIDENCE RESPIRATORY INFECTIONS AMONG 1,020 PRIVATE PATIENTS

TYPE	UNDER 1 YR.	1-3 YR.	3-5 YR.	5-7 YR.	7-9 YR.	9-12 YR.	TOTAL
Upper	89	178	98	70	27	27	489
Lower	10	18	14	20	5	4	71
Total respiratory infections among 1,020 records							560 (55%)

Included among diseases of the upper respiratory tract are rhinitis, pharyngitis, tonsillitis, and catarrhal otitis media in which myringotomy was not performed. Purulent otitis media was considered separately as a complication and is classified accordingly. The group considered as diseases of the lower respiratory tract is composed of pneumonia (all types), bronchitis, pleurisy, and pulmonary tuberculosis. It does not include a consideration of bronchial asthma and similar allergic conditions primarily involving the upper or lower respiratory tract.

TABLE III

RESPIRATORY DISEASES (INCLUDING NOSE, THROAT, AND EAR CONDITIONS)

HOSPITAL AND DISPENSARY	PRIVATE PRACTICE	PRIVATE AND HOSPITAL
Baltimore, Md.	Durham, N. C.	
Arena and Harris	A. H. London, Jr.	Miami, Fla.
147,369 cases	3,224 cases	3,743 cases
35.2%	37.7%	45.3%

Arena and Harris,[4] in 1935, attempted to determine the incidence of disease in children under 15 years of age by a study of 80,000 children

admitted to the Harriet Lane Home during the period 1912-1932. Of 147,369 diagnoses considered in that group, 35.2 per cent were of respiratory diseases. London found in 1937 that, of 3,224 cases in private practice at Durham, N. C., 37.7 per cent were included in the classification of respiratory infection. Analysis of the Miami group under consideration indicates that 47 per cent of 2,043 cases are diagnosed as some type of respiratory disease. The same percentage incidence (42 per cent of 1700 cases) occurred in the experience of four other Miami pediatricians (Table IV).

DURATION

Clinical observation impresses one that respiratory infections in Florida are somewhat less virulent in course but are of about the same duration as those seen elsewhere in the United States. In order to broaden the scope of experience represented in this statement a request was made of four representative pediatricians in the Miami area that they determine by a study of consecutive case records the following information:

(a) incidence of respiratory infections
(b) involvement of upper or lower tract
(c) percentage of complications and
(d) average duration

Replies are given in Table IV.

TABLE IV

STUDY OF 1,700 CONSECUTIVE CASE RECORDS—OFFICE PRACTICE

PEDIATRICIAN	NO. OF CASES	INCIDENCE RESPIRATORY INFECTION		TYPE		COMPLICATIONS PER CENT	AVERAGE DURATION
		NO.	PERCENTAGE	UPPER	LOWER		
C. L. Kennon	400	100	25	60	40	27.0	3-7 days
G. N. Leonard	400	172	43	149	22	16.0	3-7 days
W. W. McKibben	100	45	45	40	5		
L. W. Whelchel	800	440	55	396	44	12.6	5-7 days

Many parents do not desire repeated visits from a pediatrician for treatment of an uncomplicated upper respiratory infection suffered by their children. Office records do not, therefore, constitute an accurate criterion by which to determine the actual duration of illness. Many of these patients are ambulatory outdoors before coryzal symptoms have subsided or subfebrile temperatures become normal. The statement that the course of infection is milder but of about the same duration as observed in other sections of the United States is based necessarily upon the combined clinical experiences and observation of several pediatricians resident in the Miami area.

COMPLICATIONS

The occurrence of complications apparently varies with the type of causative organism. During a short epidemic one finds many cases of diarrhea, purulent otitis media, or pulmonary pathology. Table V represents the incidence and classification of complications encountered among the original group of 405 hospital cases and 560 office or home patients.

TABLE V

COMPLICATIONS

CLASSIFICATION	HOSPITAL GROUP—405		PRIVATE GROUP—560	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Otitis media (Purulent)	31	7.6	96	17.1
Sinusitis (All types)	3	0.7	34	6.0
Nephritis (All types)	10	2.5	4	0.7
Mastoiditis	3	0.7		
Cardiovascular	7	1.7	6	1.0
Empyema	6	1.5		
Gastrointestinal	8	1.9	22	3.9
Miscellaneous	3	0.7	2	0.4

MORTALITY

Deaths in the hospital group totaled forty-six (11.3 per cent). These are classified according to age groups in Table VI. It will be noted that all deaths under the age of 1 year were attributed to pneumonia.

Due to the fact that nearly all seriously ill children in an urban area can be hospitalized if necessary, the mortality rate in the private practice series is extremely low. Among the entire series of 560 cases in this classification, one death occurred in an infant aged 8 months, who had bronchopneumonia. Conversely, the mortality rate among the hospitalized patients is increased for the same reason. The combined mortality rate for the entire series is relatively low (4.87 per cent). The chief cause of death was pneumonia.

TABLE VI

MORTALITY OF HOSPITAL GROUP CLASSIFIED ACCORDING TO AGE (11.3 PER CENT)

DIAGNOSIS	UNDER 1 YR.	1-3 YR.	3-5 YR.	5-7 YR.	7-9 YR.	9-12 YR.
Pneumonia (All types)	16	11	3	4		1
Endocarditis		1				
Pharyngitis (Streptococcal)		2		1		
Miliary tuberculosis			1	1		
Mastoiditis			1			
Septicemia (All types)			1	1		
Encephalitis						1
Pulmonary abscess						1

COMMENT

Nichol[5] has called attention to the infrequency of acute rheumatic fever and rheumatic carditis in this area. Mastoiditis seldom occurs,

Among 14,300 admissions to the St. Francis Hospital at Miami Beach during the past seven years, the diagnosis of mastoiditis appears 38 times, an incidence of about 0.27 per cent.[6]

A concentration of sinus sufferers from all parts of the country during the winter season materially affects the incidence of sinusitis among this group of patients. Acute sinusitis responds well to conservative management, and, almost without exception, the sufferers from chronic sinusitis find symptomatic improvement. Children of this area frequent public swimming pools during the entire year. Because of this fact, the percentage incidence of sinusitis may be affected.

MANAGEMENT

Management of the acute respiratory infection is essentially the same in Florida as in other sections of the United States. Convalescence is shorter, probably being influenced favorably by the equable climate, an atmosphere free from industrial smoke, and the uncrowded mode of outdoor living. The low altitude and high humidity are not advantageous to the child with hypertrophied, chronically infected lymphoid tissue in the upper respiratory tract.

This lower coastal region of Florida with its subtropical environment lures many sufferers with chronic or recurrent colds, who are seeking relief by means of climatic therapy. Metzger[7] has warned that many of these whose pathologic condition is primarily allergic in character either obtain no relief or become worse in their new environment. Some show improvement or complete recovery. Aided by the habits of living practiced in a twelve-month outdoor season and a high year round ultraviolet radiation, many children show far less susceptibility to colds. Annually, there are thousands of children who congregate here in an effort to obtain relief from recurrent respiratory infections. It is commonly observed that there is a rapid diminution in the number of these infections among the native Florida children immediately following the winter season and again at the close of the schools in June.

SUMMARY

1. Comparison of approximately 1000 hospital records with a similar group of patients attended at office or home indicates that a large percentage (47 per cent in this series) of pediatric practice in Florida is concerned with respiratory infections.

2. This high incidence may be influenced by seasonal influx of tourists and by similar factors generally observed in a resort center.

3. The combined clinical experience of several pediatricians of the Miami area confirms the impression that these respiratory infections are of about the same average duration but are less virulent in their course than elsewhere.

4. Complications occur infrequently but are often quite severe in intensity. The combined mortality rate for both groups in this series is 4.87 per cent.

5. Conservative medical management of most respiratory infections here evokes a favorable response.

CONCLUSION

Analysis and tabular classification of 2,043 clinical records indicates a relatively high incidence of respiratory infections among the children of south Florida.

The usual course and infrequent occurrence of severe complications is probably influenced favorably by mild climatic conditions and by freedom from sudden extremes of temperature.

REFERENCES

1. Kneeland, Y., Jr., and Dawes, C. F.: J. Exper. Med. **55**: 735, 1932.
2. Spiesman, L. G., and Arnold, L.: Am. J. Digest. Dis. & Nutrition **4**: 438, 1937.
3. Taylor, H. M., and Dyrenforth, L. Y.: J. A. M. A. **111**: 1744, 1938.
4. Arena, Jay M., and Harris, R. R.: South. Med. & Surg. **97**: 520, 1935.
5. Nichol, E. S.: Am. Heart J. **9**: 63, 1933.
6. Leonard, G. N.: Personal communication.
7. Metzger, Frank: J. A. M. A. **112**: 29, 1939.

227 AVENUE ARAGON

IN VITRO EFFECT OF PECTIN AND NICKEL PECTIN ON BACTERIAL GROWTH

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I. EFFECT OF PECTIN

THE old, empirical folk remedy of treating diarrhea by feeding raw apple was elevated to the rank of a recognized medical procedure by Moro[1] and Heisler.[2] The modus operandi of this therapy is vague. Moro suggested that the therapeutic value of this fruit may be due to its tannic acid content. Malic acid and mechanical cleansing of the intestinal tract were explanations proposed by Heisler. Scheer, who successfully fed "agar milk"[3] for diarrhea, thought that indigestible bulk[4] was more important. The cellulose and pectin in apples are considered to be the therapeutic ingredients by Malyoth.[5] The treatment of diarrhea with pectin and agar was first suggested in this country by Winters and Tompkins.[6]

Among the hypotheses proposed to explain the favorable action of pectin in diarrhea are (1) that pectin absorbs and sweeps out toxins and bacteria from the intestinal tract;[7, 8] (2) that pectin as a source of galacturonic acid is not only an important detoxifying agent, but, through its influence on the pH of the intestinal tract's contents, it also helps control the intestinal flora;[9] (3) that pectin is soothing and healing to the inflamed and ulcerated intestinal canal;[10] and (4) that pectin exerts a bactericidal effect.[11] This last theory has been under investigation by us for several years, and in a preliminary report,[12] we were unable to confirm the bactericidal effect of pectin. However, the effect of this substance on bacterial growth appeared to be of sufficient importance to warrant more detailed studies.

PROCEDURE

After testing various techniques, we have developed a satisfactory method, which is a combination and modification of two previously described procedures,[13, 14] for determining the effect of pectin on bacterial growth.

Using a standard concentration of 1 per cent, each pectin was aseptically added very slowly to sterile nutrient broth, pH 6.5, with constant agitation to prevent lumping and then heated in an Arnold steamer for 5 minutes. The respective hydrogen ion concentrations of the resulting pectin broths (which we define as the "natural" pH) were from 3.9 to 5.5. A duplicate series of pectin broths was similarly prepared, save that the pH of each was adjusted to 6.5. For each pectin broth two controls were used, one being sterile nutrient broth adjusted to the "natural" pH of the respective pectin broth solutions, the other being sterile nutrient broth at pH 6.5. All pH determinations were made with a glass electrode.

From the Bacteriologic Laboratory, Mead Johnson & Company.

A sample of pectin was tested by inoculating 100 c.c. of each of the above broths, contained in cotton-stoppered flasks, with 1 c.c. each of the same 24-hour nutrient broth culture of the test organism and incubated at 37° C. The test organism used was a typical culture of *Esch. coli* isolated from feces. Plate counts were made after 0, 24, and 48 hours' incubation.

RESULTS

Thirteen different commercial pectins, ranging in grade* from 100 to 315 and prepared from both citrous fruits and apples, were investigated. Some of the pectin samples contained a filler of fermentable material added to standardize the grade, a recognized manufacturing practice. Chemical analyses showed that the mineral contents of the thirteen samples varied considerably. Nickel in small amounts (0.12 to 0.16 per cent) was found only in the pectin (3 samples) submitted by one manufacturer, who informed us that this metal, as well as a filler, was added during manufacture.

In nine of the pectin broths with "natural" pH from 4.9 to 5.5, designated as Group 1, and, likewise, in the control broths at the corresponding "natural" pH, large increases of the inoculated *Esch. coli* were observed. This effect of pectin is illustrated in Table I by the data of pectin No. 1, representative of this group. In the remaining four pectin broths with "natural" pH from 3.9 to 4.4, designated as Group 2, and, likewise, in the control broths at the corresponding "natural" pH, marked decreases of the test organism occurred. This is demonstrated by the data for pectin No. 10, Table I. The data for pectin No. 10 also show that a pectin broth which is bactericidal at the "natural" pH supports luxuriant bacterial growth when the pH is adjusted to 6.5. Similar results were obtained with the control broths which contained no pectin.

TABLE I

EFFECT OF PECTIN IN NUTRIENT BROTH ON ESCH. COLI*

BROTH WITH	TREATMENT	pH AFTER		PLATE COUNTS AFTER	
		0 HR.	48 HR.	0 HR.	48 HR.
No. 1 pectin	"natural"	5.1	6.7	2,500,000	250,000,000
Control		5.1	7.4	2,500,000	200,000,000
No. 1 pectin	adjusted	6.5	7.2	2,500,000	500,000,000
Control		6.5	7.9	2,500,000	230,000,000
No. 10 pectin	"natural"	4.3	4.6	2,500,000	0
Control		4.3	4.8	2,500,000	60
No. 10 pectin	adjusted	6.5	7.2	2,500,000	350,000,000
Control		6.5	7.8	2,500,000	220,000,000

*Pectin is in 1 per cent solution in all tests.

In fact, in all thirteen pectin broths adjusted to pH 6.5, and, likewise, in the control broths at the same pH, the inocula showed large increases in counts after incubation. These findings indicate that it is primarily

*Grade refers to the number of pounds of sugar which one pound of pectin will jell under standard conditions.

the acidifying effect of a pectin which influences the bacterial growth. Data in Table I show that any inhibiting effect of pectin on bacterial growth can be duplicated simply by the addition of HCl to nutrient broth. It is to be noted from the data that the increases in the bacterial counts were accompanied by increases of pH.

TABLE II

EFFECT ON ESCH. COLI OF PECTIN CONTAINING CARBOHYDRATE FILLER IN NUTRIENT BROTH

BROTH WITH	TREATMENT	pH AFTER			PLATE COUNTS AFTER		
		0 HR.	24 HR.	48 HR.	0 HR.	24 HR.	48 HR.
No. 9 pectin	"natural"	5.0	4.7	4.7	3,000,000	50,000,000	35,000,000
No. 9 pectin	adjusted	6.5	4.7	4.6	3,000,000	270,000,000	160,000,000

Many commercial pectins contain varying amounts of added fermentable filler and the presence of this extraneous material will definitely change the bacterial picture under the conditions of this test. Such a pectin (No. 9, Table II) may have on solution a pH insufficiently low to inhibit bacterial growth. However, with the ensuing multiplication of organisms, acid is produced which results in a lowered bacterial count during the second 24-hour incubation period. Likewise, when the "natural" pH is adjusted to 6.5, the organisms grow luxuriantly for the first 24 hours, but the elaboration of acid causes a drop in both pH and bacterial count by the end of 48 hours' incubation. From the data in Table II the importance not only of determining the pH at the time of inoculation but also during and at the end of incubation is evident.

It is noted that all thirteen pectin samples (both with and without added fermentable filler) behaved exactly like those chosen for illustrative purposes and presented in Tables I and II.

DISCUSSION

We have standardized a 1 per cent pectin solution in nutrient broth, since the higher the concentration, the more difficult it is to dissolve the pectin. Furthermore, a difficultly soluble pectin in higher concentration is dissolved only by severe heat treatment, which tends to break down the pectin molecule. However, we have tested the more soluble pectins in solutions up to 5 per cent with results similar to those obtained with the standard 1 per cent solution. Although only the more difficultly soluble pectins required heat to secure complete solution, all pectin broths received the same, moderate heat treatment, for uniformity. After dissolving the pectins, all pH adjustments were made at room temperature to eliminate degradation of the pectin by heat and alkali.

Esch. coli, in the absence of fermentable material, thrives on nitrogenous substance, thus producing an alkaline reaction and raising the pH.

On the other hand, in the presence of fermentable material, it produces acid, thereby lowering the pH. It is known that this organism, given the opportunity, will produce sufficient acid to kill itself.

The power of this organism to increase or decrease the pH, according to conditions, is well illustrated in this study. For example, in the presence of pectin which does not contain significant amounts of fermentable material, the organism utilized the nitrogenous material of the media with a resultant rise in pH. On the other hand, in the presence of a filled pectin, the fermentable material was attacked, resulting in a sufficient drop in pH to cause the number of organisms to diminish. The inhibiting effect of low pH on bacterial growth has long been recognized, and the similar effect of pectin is merely an additional illustration of this same principle.

Therefore it is important to determine not only initial pH but also the pH during and at the end of incubation. For it is apparent that it is impossible to interpret properly the data secured in this type of study if only the pH at the time of inoculation is considered.

SUMMARY

1. A method is described for testing the effect of pectin and filled pectin on bacterial growth, using *Esch. coli* as the test organism. Thirteen different commercial pectins of widely varying grades and types were studied.

2. No reason was found to believe that pectin per se is bactericidal. In nine of the samples (pH 4.9 to 5.5) marked increases of the inocula were observed. When the pH was low (3.9 to 4.4), four samples showed marked decreases in counts. The broths, without pectin, but with similar pH, showed similar changes in growth.

3. When pectin broths were adjusted to pH 6.5, all inocula increased to approximately the same extent as in the control broths, save that the growth was modified by the presence in the pectin of fermentable filler.

4. It is evident that whatever unfavorable effect on bacterial growth is noted in pectin broth is the result of acidity.

II. Effect of Nickel Pectin

It has been reported[13, 15] that nickel is bactericidal at low concentrations. Three samples of filled pectin reported in Part I contained 0.12 to 0.16 per cent nickel, which resulted in a concentration of 0.0012 to 0.0016 per cent nickel in the standard 1 per cent pectin broth. These particular samples of pectin were not germicidal and were found to have the same influence on bacterial growth as nickel-free pectins of the same acidity and containing approximately the same amount of fermentable filler. Therefore we were interested in determining what percentage of nickel in pectin would be necessary to show a bactericidal effect.

PROCEDURE

Three different nickel-free samples of pectin were selected as follows: (1) citrous pectin, 195 grade; (2) apple pectin, 132 grade; and (3) citrous pectin, 100 grade, which contained a fermentable filler. One per cent of the sample was dissolved in nutrient broth as described in Part I. The "natural" pH of each of these pectin broths was 5.0. Nickel chloride was added to each of the pectin broths to give concentrations of metallic nickel ranging from 0 to 0.1 per cent, the actual concentrations being: 0, 0.001, 0.0015, 0.003, 0.006, 0.01, 0.03, 0.06, and 0.10 per cent. One series of these various concentrations was adjusted, because of the acidifying effect of the added nickel chloride, to pH 5.0, and a duplicate series was adjusted to pH 6.5.

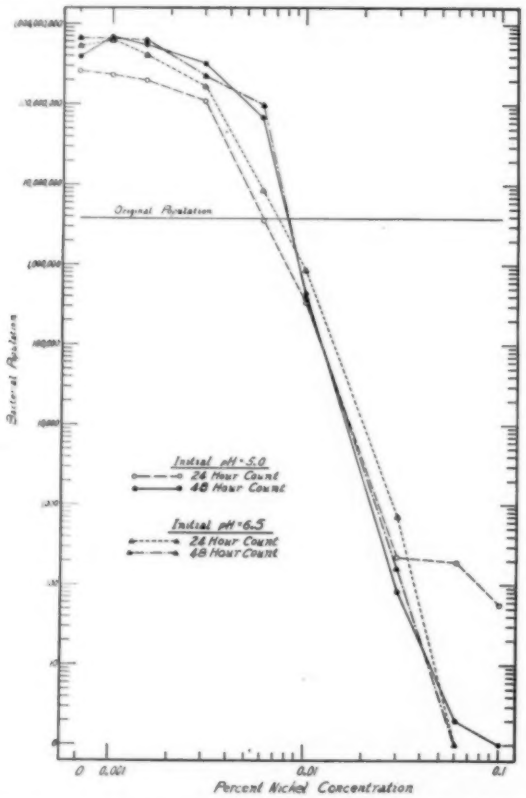

Fig. 1.—Graph showing numbers of *Esch. coli* in control nutrient broth at different nickel concentrations. (Plotted logarithmically.)

As controls for the first two pectin samples listed above, identical nickel concentrations in nutrient broth were prepared at pH 5.0 and 6.5. As a control for the pectin containing a fermentable filler, the concentrations of nickel were added to 0.5 per cent dextrose nutrient broth at the two stated hydrogen ion concentrations. This percentage of dextrose in the broth approximates the amount of fermentable filler contributed by the filled pectin in 1 per cent solu-

tion. These broths were inoculated, incubated, and plated after 0, 24, and 48 hours as described in Part I. The pH determinations were made after each period, with the glass electrode.

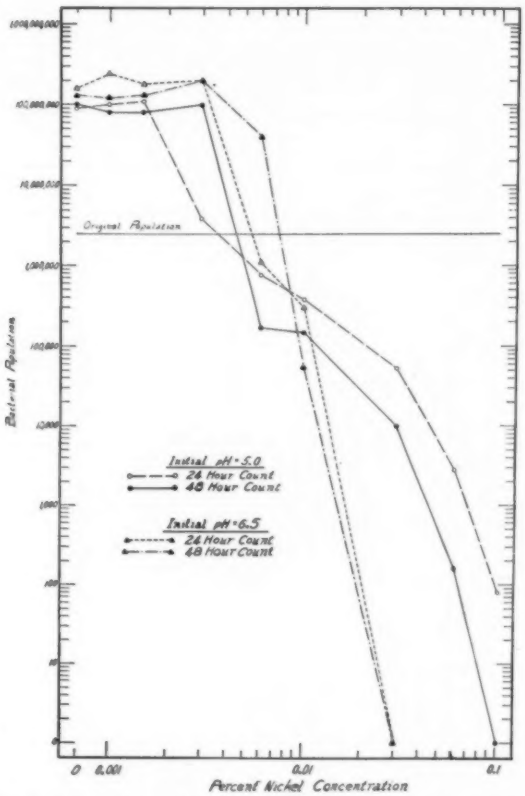

Fig. 2.—Graph showing numbers of *Esch. coli* in 0.5 per cent dextrose control nutrient broth at different nickel concentrations. (Plotted logarithmically.)

RESULTS

The action of nickel in the sugar-free control broths on the growth of *Esch. coli* is shown in Fig. 1, and its action in dextrose control broths is given in Fig. 2. It is to be noted that in each illustration one set of these broths had an initial pH 5.0 and the other, 6.5. Considering the nickel concentrations which cause the bacterial counts to drop below the original population as bactericidal, one may see that all curves cross the original population line at nickel concentrations less than 0.01 per cent. Above the original population line the retarding effect of nickel is evident from the breaks in the population curves between 0.003 and 0.006 per cent.

The same general shape of the population curves in Figs. 1 and 2 show that similar forces are influencing bacterial growth. Although these factors have the same influence in corresponding portions of the curves, nevertheless, their influence varies along the same curve. At the lower nickel concentrations growth of the test organism occurred, resulting in a change of the initial pH during incubation. As the nickel concentration increased, the bacterial growth was diminished,

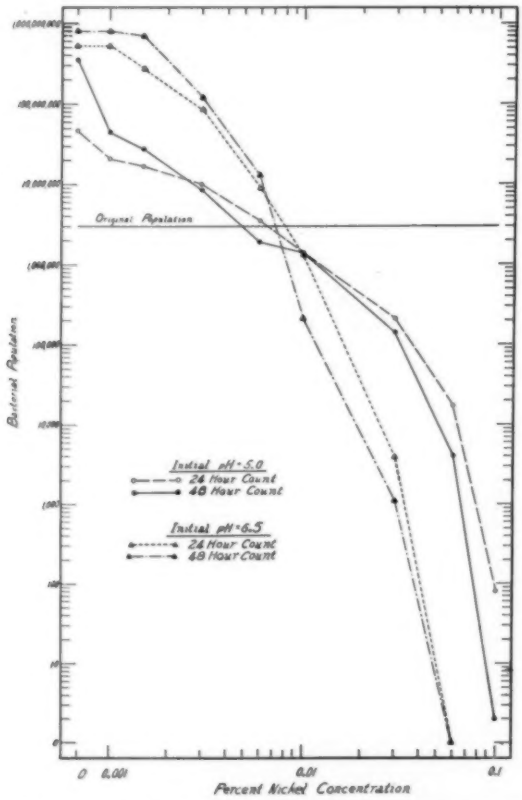

Fig. 3.—Graph showing numbers of *Esch. coli* in 1 per cent citrous pectin, 195 grade, in nutrient broth at different nickel concentrations. (Plotted logarithmically.)

and consequently the change in the initial pH during incubation decreased. This continued until the bactericidal range of nickel was reached where the initial pH remained practically unchanged during incubation. Thus it is seen that in each curve, pH exerted an influence at all nickel concentrations, but its importance as a determinant of the final count varied with the concentration of this heavy metal.

The action of the same concentrations of nickel in pectin broths on the growth of the test organism is shown by the curves in Figs. 3 and 4. The similarity of these curves to those obtained in the control broths (Fig. 1) is evident. The nickel concentrations at which these curves cross the original population line occupy almost the same range of nickel concentrations as do the curves of the control broths.

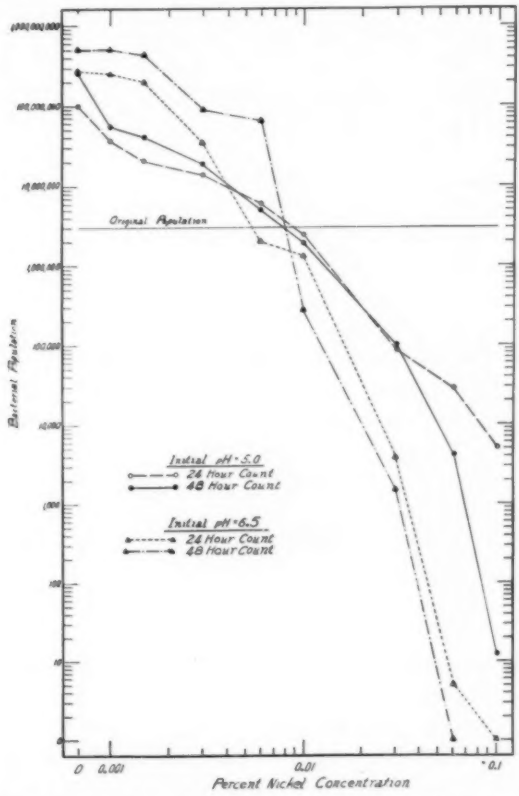

Fig. 4.—Graph showing numbers of *Esch. coli* in 1 per cent apple pectin, 132 grade, in nutrient broth at different nickel concentrations. (Plotted logarithmically.)

Determinations of pH showed again that this factor was significant for bacterial growth at the lower nickel concentrations in the presence of pectin. The hydrogen ion concentrations increased during incubation at the lower nickel concentrations; although the final pH did not increase as much as in the control broths, due to the buffer action of pectin, nevertheless, they were quite comparable to the controls. As in the control broths, in the bactericidal range of nickel the initial pH remained practically unchanged.

The action of the same nickel concentrations in pectin broths containing filler is shown in the curves of Fig. 5. The similarity of these curves to those obtained in the control dextrose broths (Fig. 2) is apparent. When the range of nickel concentrations at which these curves cross the original population line is compared with that of the control dextrose broths, it is seen that both ranges fall between approximately the same nickel concentrations.

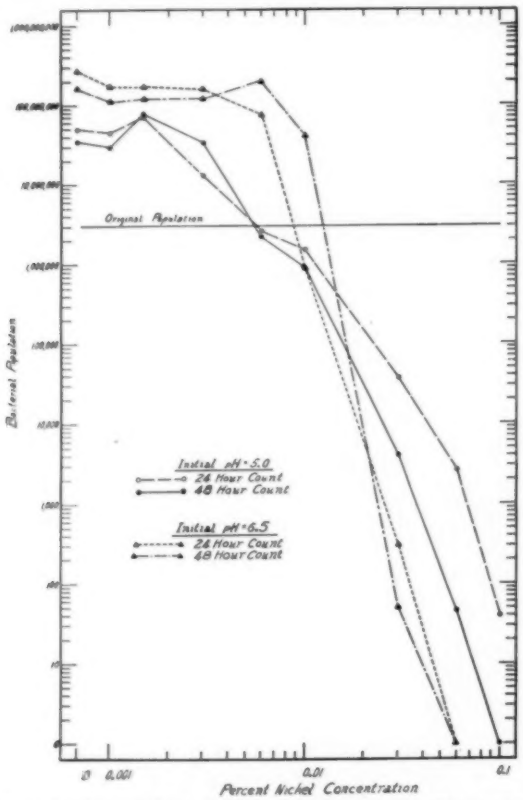

Fig. 5.—Graph showing numbers of *Esch. coli* in 1 per cent citrous pectin, 100 grade and containing a fermentable filler, in nutrient broth at different nickel concentrations. (Plotted logarithmically.)

Because these pectin broths and also the controls contained fermentable materials, in the lower nickel concentrations the pH decreased during incubation instead of increasing as in the former series. In the bactericidal range the pH remained unchanged, as it did in the controls.

DISCUSSION

In a comparison of all the curves, the narrow range of nickel concentrations at which the curves cross the original population lines is all the

more remarkable when the variety of conditions is taken into consideration: sources of pectin, pectin grades, the different mineral contents, presence and absence of fermentable filler, and various buffer values.

The influence of pH, discussed in Part I, is further demonstrated by the counts of all 0 per cent nickel broths. The original populations were approximately the same in all of these broths; however, incubation resulted in higher counts in all broths with initial pH 6.5 as compared to initial pH 5.0. This was due to the former's more nearly optimal initial pH that favored immediate growth. As was also pointed out in Part I, during incubation the pH decreased in the broths containing fermentable material, whereas in the sugar-free broths the pH increased. These pH reversals are reflected in the bacterial population curves (Figs. 1-5); in the presence of fermentable material, the 24-hour counts tended to be higher than the 48-hour counts, but in the sugar-free broths the reverse occurred.

Does the addition of pectin alter the picture obtained by nickel alone? From the study of Figs. 3, 4, and 5 the answer must be in the negative. The general appearance of all curves is so essentially similar that no value can be attributed to the pectin itself. There are, however, certain minor points of interest that should be mentioned.

In Figs. 3 and 4 it will be noted that the spread of counts at 0 per cent nickel was greater than that in the controls (Fig. 1). The pertinent fact here is that pectin had a buffering effect. In its absence (Fig. 1) the initial pH of 5.0 rapidly increased, allowing rapid multiplication. When it was present (Figs. 3 and 4), rise in pH was retarded and there was a lower bacterial count. During the second 24-hour period, the most rapid multiplication occurred because sufficient alkali had finally been produced to overcome the buffer action of pectin. In fact, this buffer effect is noticeable in all of the curves (Figs. 1-5) at the lower nickel concentrations where pH exerts a significant influence on growth.

These bacterial population curves show that, at the lower nickel concentrations, the unfavorable influence of this metal on bacterial growth is more marked in the broths at an initial pH 5.0. At the higher concentrations, its toxic effect was more marked in the broths with an initial pH 6.5. However, previously reported findings indicated that nickel is more toxic in a more acid range.[16]

In this study little or no evidence was obtained showing the stimulating effect of small quantities of nickel on bacterial growth, for the lowest concentrations used are just above the upper stimulating concentrations reported by Hotchkiss.[13] In addition, Hotchkiss studied the bactericidal effect of metals, including nickel, on bacterial growth by

adding various concentrations to broth as we did. Although she determined the resulting bacterial populations by a turbidimetric method, whereas we used the plating technique; yet, so far as the data are comparable, our findings confirm hers.

In addition to nutrient agar, duplicate plates were poured using violet red bile agar,[17] a specific differential medium for *Esch. coli.* Practically identical counts were obtained on these two media, and no foreign types developed on the differential medium. It is evident that the size of the inoculum enabled the *Esch. coli* to overgrow contaminants from any source. Therefore, only counts on nutrient agar are reported.

Although these data were obtained in vitro, nevertheless, they offer some basis for hypothesis concerning the action of ingested pectin. They show that any unfavorable influence on bacterial growth exerted by pectin is by means of its acidity and the consequent influence on the pH, and that above pH 4.5 the growth of *Esch. coli* is little retarded. Since the intestinal contents are usually at a pH higher than 4.5 and are also well buffered, it would be expected that ingested pectin would have less influence on the pH of the intestinal contents than it has in nutrient broth. Thus, this work demonstrates that pectin per se does not markedly retard the growth of intestinal bacteria. Hence it may be assumed that pectin does not have any bactericidal effect in the intestine. The other question is the concentration of nickel which would be required in the intestinal tract to exert bactericidal action. Again applying in vitro studies, it would appear that concentrations of nickel between .006 and .01 per cent in the intestine must be attained before any marked inhibition of bacterial growth could be expected.

SUMMARY

1. The effect of nickel in various concentrations on bacterial growth, using *Esch. coli* as the test organism, was studied in the absence and presence of pectin.

2. The bactericidal effect of nickel varied directly with its concentration. The pH of the media, the buffer effect of pectin, and the presence or absence of fermentable material modified but did not essentially change this effect.

GENERAL CONCLUSIONS

To the extent that pectin, regardless of its grade, affects the pH, modification of bacterial growth can be expected. Growth in pectin solution flourishes with many types of pectin because these types do not lower the pH sufficiently. In all cases where the pH of a pectin solution was adjusted to a range favorable for *Esch. coli,* growth was abundant.

Bactericidal action of nickel varies directly with its concentration. No essential difference in toxicity was shown whether this heavy metal

was in nutrient broth or in broth containing pectin. Therefore, any bactericidal effect of pectin containing nickel is due solely to this heavy metal.

Acknowledgment is made for the courtesy of L. N. BeMiller in making the chemical determinations.

REFERENCES

1. Moro, E.: Klin. Wchnschr. **8**: 2414, 1929.
2. Heisler, A.: Klin. Wchnschr. **9**: 408, 1930.
3. Scheer, K.: Acta paediat. **22**: 421, 1938.
4. Scheer, K.: Kinderkrankheiten (ohne Infektionskrankheiten) und Ernährungslehre, Dresden and Leipzig, 1935, Theodor Steinkopff, pp. 50-53.
5. Malyoth, G.: Klin. Wchnschr. **10**: 1159, 1931; **13**: 51, 1934.
6. Winters, M., and Tompkins, C. A.: Am. J. Dis. Child. **52**: 259, 1936.
7. Baumann, T.: Klin. Wchnschr. **11**: 1261, 1932.
8. Ziegelmayer, W.: Klin. Wchnschr. **15**: 19, 1936.
9. Manville, I. A., Bradway, E. M., and McMinis, A. S.: Am. J. Digest. Dis. **3**: 570, 1936; **5**: 428, 1938.
10. Manville, I. A., Bradway, E. M., and McMinis, A. S.: Canad. M. A. J. **36**: 252, 1937.
11. Tompkins, C. A.: Personal communication.
12. Prickett, P. S., and Miller, N. J.: Proc. Soc. Exper. Biol. & Med. **40**: 27, 1939.
13. Hotchkiss, M.: J. Bact. **8**: 141, 1923.
14. Haynes, E., Tompkins, C. A., Washburn, G., and Winters, M.: Proc. Soc. Exper. Biol. & Med. **36**: 839, 1937.
15. Haynes, E., Tompkins, C. A., Crook, G. W., and Winters, M.: Proc. Soc. Exper. Biol. & Med. **39**: 478, 1938.
16. Arnold, L.: Am. J. Digest. Dis. **6**: 104, 1939.
17. Miller, N. J., and Prickett, P. S.: J. Dairy Sc. **21**: 559, 1938.

AN UNUSUAL CASE OF EPHEDRINE POISONING

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ALLERGIC reactions and toxic effects following the use of ephedrine, either by injection or topical application, have been frequently reported. Bullen and associates[1] state that the reactions may occur within a few hours after the first dose of the drug or only after a nasal spray containing ephedrine has been used for several months. The most common allergic response seems to appear on the skin, where dermatitis venenata and eczematous and erythematous lesions, both local at the point of the application and generalized, have been described.[2-4] Some of the investigators report positive scratch or patch tests as evidence of cutaneous hypersensitivity to ephedrine. Among the chief toxic effects mentioned in the literature are cardiovascular symptoms such as acute precordial pain with palpitation and profuse sweating,[5] tremors of the extremities, flushing all over the body and a dull sensation in the region of the temples, faintness, loss of muscular tone, irregular and rapid pulse, widely dilated pupils, feeble heartbeats, and dyspneic type of respiration. Dysuria and urinary retention are frequently mentioned as accompanying features.[5-7] Occasionally gastrointestinal symptoms are observed following the use of large doses of ephedrine or ephetonine, such as nausea, anorexia, constipation, and marked abdominal distention.[8] Chen and Schmidt,[9] who saw no untoward effects in men following the application of single doses of 400 mg. of ephedrine or 150 mg. repeated every three hours day and night, describe among the toxic effects perspiration, chill, palpitation, weakness, dizziness, nervousness, tremor, nausea, and epigastric discomfort.

The paucity of clinical reports regarding the toxicity of the drug in childhood in spite of its widespread use prompts the publication of the following report of ephedrine poisoning in a case which shows some unusual features:

J. F., 5 months old, when first seen, had an acute nasopharyngitis, afebrile, but with sufficient watery nasal secretion to make nursing very uncomfortable. Two drops of a 3 per cent aqueous solution of ephedrine sulfate into each nostril every four hours was prescribed. Thirty-six hours later the mother noticed extreme nervousness and irritability. Examination shortly afterwards revealed an acutely ill child, lying with retracted head in the position of opisthotonos. There were paroxysmal contractions of the body musculature, lasting for several seconds and appearing within intervals of about 10 minutes. There was a considerable degree of tonic spasm between paroxysms. Temperature was 101° F.; the face was pale; the knee jerks and deep reflexes were increased; and the skin was cold and clammy. The pupils were widely dilated; the palatal reflexes were absent; and the child could or would not swallow. A careful questioning elicited the fact that the mother had been so pleased with the favorable effect of the drug that she employed the nasal

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instillation at least once an hour. She estimated that she gave twenty doses of three drops of the 3 per cent solution in each nostril within thirty-six hours. This approximately corresponds to 2 c.c. of the 3 per cent solution, equal to 0.06 gm. or about 1 gr. in each nostril. Treatment with morphine sulfate, 1/64 gr. hypodermically, and a gastric lavage were successful, and the symptoms ceased after eight hours. Recovery was uneventful.

The interesting feature is the combination of the clinical picture of atropine poisoning with that of strychnine poisoning. The rapid pulse, the inability to swallow, the dilated pupils, the restlessness, and irritability are well-known features of overdoses of atropine. The increased reflex action and the spasms of the body muscles at regular intervals with incomplete relaxation between the seizures are commonly found in strychnine poisoning.

The dose of 2 gr. of ephedrine sulfate within thirty-six hours seems to be large for a 5-month-old child. However, since the drug was given intranasally, presumably only a part of it was absorbed. Anderson and Homan[8] report marked restlessness in two infants, 5 and 6 months of age, respectively, following the use of 1/8 gr. of ephedrine internally night and morning. According to Pak and Read,[10] the minimum lethal dose of ephedrine in dogs and rabbits is from 50 to 70 mg. per kilogram of body weight. Similar figures are given by Chopra and Mukherjee.[5] From this, it might be inferred that in adults 4 to 5 gm. of ephedrine given at a single dose would be fatal. The doses commonly used are much smaller and, therefore, less toxic. The margin of safety is wide.

The pharmacologic action of ephedrine is similar to that of adrenalin. The clinical symptoms may be explained by the sympathomimetic effect of the drug. In our case the stimulation of the central nervous system was particularly marked. The sympathetic stimulation was furthermore apparent in the dilatation of the pupils and the rapid heartbeat. No significant gastrointestinal symptoms were noted.

SUMMARY

Report is made of a case of a 5-month-old child showing symptoms of ephedrine poisoning within thirty-six hours following the nasal instillation of 2 gr. of the drug. The clinical picture showed a combination of features common to atropine poisoning with those commonly observed in strychnine poisoning.

REFERENCES

1. Bullen, S. S., et al.: J. Allergy **3**: 485, 1932.
2. Ayres, S., and Anderson, N. P.: J. A. M. A. **97**: 437, 1931.
3. Hollander, L.: J. A. M. A. **106**: 706, 1936.
4. Abramowitz, E. W.: Brit. J. Dermat. **45**: 225, 1933.
5. Chopra, R. N., and Mukherjee, B.: Indian M. Gaz. **68**: 622, 1933.
6. Balyeat, R. M., and Rinkel, H. J.: J. A. M. A. **98**: 1545, 1932.
7. Edger, J. N.: New Zealand M. J. **27**: 232, 1928.
8. Anderson, W. D., and Homan, C. E.: Am. J. M. Sc. **174**: 738, 1927.
9. Chen, K. K., and Schmidt, C. F.: J. A M. A. **87**: 836, 1926.
10. Pak, C., and Read, B. E.: Chinese J. Physiol. **3**: 81, 1929.

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FATAL LEAD POISONING IN A NURSING INFANT DUE TO PROLONGED USE OF LEAD NIPPLE SHIELDS

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LEAD poisoning in very early infancy is uncommon. Congenital poisoning has been described, and a few definite cases of placental transmission have been recorded.[1] The commonest causes, however, are from cosmetics or ointments applied to the mother's face or breasts. Cases due to lead-containing ointments used for fissured nipples have been reported by numerous authors.[2] Kato,[3] writing on lead meningitis, reviews the work of Japanese authors who discovered that lead-containing face powders used by the mother gave rise to many cases of poisoning of infants. He also mentions cases due to lead-containing lotion used on the nipple; lead incorporated in the glass of nursing bottles; lead frame holding the nursing bottle; lead-containing rubber nipple; lead plasters; and lead-containing dusting powders. The burning of old automobile battery casings for fuel was an etiologic factor in certain cases.[4] Lead in toys or painted objects licked or sucked by the infant may be blamed also. In older infants and children, so-called pica is the commonest cause; thus Blackman,[5] in his excellent article on lead encephalopathy, collected twenty-two cases, most of which were due to this form of ingestion.

The occurrence in private practice of a fatal case of lead poisoning in a 4-month-old infant, due to prolonged use by the mother of lead nipple shields, prompted us to publish the case in order again to emphasize the danger incurred by this pernicious practice.

CASE REPORT

A white male baby, aged 4 months, was seen at 5 P.M., Oct. 30, 1938, because of a convulsion of several hours' duration. The baby had been born of healthy parents June 27, 1938. Labor had been normal. Delivery was normal and noninstrumental. Birth weight was 7 pounds and 14 ounces. There was no apparent birth injury and no difficulty in resuscitation. The infant was breast-fed and gained well. At 3 months of age the child was examined and found to be in excellent condition except for slight pallor for which saccharated carbonate of iron, 1.3 gm. daily, was prescribed.

On Oct. 29, the child appeared less happy than usual. He stared at objects vacantly and did not appear playful. On the morning of Oct. 30 the infant vomited his breast feedings. As he did not appear ill, he was taken out in an automobile. In the early afternoon he again vomited and had twitching movements of his extremities, followed by stupor. He was immediately brought home and seen by one of us (M.H.B.) at 5 P.M.

There was no history of colic and no vomiting prior to Oct. 30. The stools were normal in character and number. The temperature was normal. The child did not seem to have been more irritable before the onset of symptoms on the previous day.

On examination the infant was found to be unconscious. The head was not in opisthotonos but was turned to the left. The eyes were deviated toward the left, and the pupils were equal and widely dilated. The fontanel was open and definitely bulging. There was no neck rigidity or Kernig's sign. The right upper and lower extremities were held in flexion with the right hand clenched. The left upper and lower extremities were extended. The superficial and deep reflexes were all exaggerated. There was no clonus. The throat and ears were normal. The heart and lungs were normal. The abdomen was soft and no masses were palpable. The liver and spleen were not palpable. Pallor was striking.

The mother was carefully questioned regarding a history of trauma, but no information was elicited. The extreme pallor, the normal temperature, normal stools, absence of any history of trauma, absence of any signs of hemorrhagic disease, and the lack of hemorrhage in the eye grounds made us suspicious of some form of poisoning, lead being thought the most likely.

On further questioning, it was learned that during the infant's neonatal period the mother had developed fissuring of the nipples, for which she had been advised to use lead nipple shields. These had been applied to the breasts every day up to the time of the present illness. Before each nursing the mother had carefully washed the nipples with a boric acid solution. However, during the week prior to the onset of symptoms, the mother had a mild upper respiratory infection during which she often failed to wash the nipples before nursing.

On obtaining this information a provisional diagnosis of lead encephalopathy was made and a blood smear taken. This showed very extensive basophilic stippling of the red cells. The child was then hospitalized at the Mount Sinai Hospital, and a lumbar puncture was done. The fluid was under markedly increased pressure. About 10 c.c. of xanthochromic fluid was withdrawn. Following this procedure the child became quieter, and the fontanel became flat. In several hours convulsive movements were again marked and the fontanel was bulging. Large doses of sedatives were given in an attempt to stop the twitching. Codeine sulfate, chloral hydrate, sodium bromide, sodium luminal, and sodium amytal were given with very little effect on the convulsive movements. The infant was given a blood transfusion and concentrated sucrose (25 per cent) intravenously. In addition 10 c.c. of 10 per cent disodium phosphate was given three times daily. The child never recovered consciousness and on the fourth day developed pulmonary edema and died.

Laboratory examination of the blood revealed hemoglobin, 53 per cent; red blood cells, 3,900,000; white blood cells, 11,900; polymorphonuclear cells, 63 per cent; large lymphocytes, 1 per cent; small lymphocytes, 34 per cent; monocytes, 2 per cent.

There was marked basophilic stippling. Urine showed a heavy trace of albumin and hyaline and granular casts. Spinal fluid was xanthochromic. No cells were seen. The Pandy test was positive. A specimen of venous blood was found to contain 0.11 mg. lead in 100 c.c. whole blood (0.06 mg. is considered the upper limit of normal).*

X-ray examination showed a marked increase in density of the distal ends of the diaphyses of all the long bones and a peripheral density of the flat bones of the feet (Fig. 1).

NECROPSY†

The body was that of a well-developed and well-nourished 4-month-old white male infant in partial rigor mortis. There was marked waxy pallor of the skin and

*The chemical examination of the blood was kindly done for us by Dr. Benjamin Kramer who saw the case in consultation.

†Done by Dr. Arthur C. Allen and Dr. Joseph Globus.

mucous membranes. Moderate dependent lividity was present. The posterior fontanel was closed. The mouth was edentulous, and there was no lead line on the gums. There was no jaundice or purpura. There was a minimal pitting of the pretibial tissues.

Abdomen.—The panniculus adiposus was about 1.5 cm. thick. The abdominal cavity contained about 15 c.c. of clear, odorless, amber-colored fluid. The peritoneal surfaces were smooth and glistening. The liver extended two fingerbreadths below the right costal border in the midclavicular line. The spleen was above the left costal border. The right dome of the diaphragm ascended to the fourth intercostal space, and the left cupola reached the fifth rib. The femoral veins "milked" freely.

Fig. 1.—Radiographs illustrating dense shadows of lead deposition at the epiphyses of both the upper and lower extremities.

Thorax.—Both pleural cavities were dry and both lungs were nonadherent.

Heart.—The heart weighed 40 gm. The pericardial sac contained about 10 c.c. of straw-colored fluid. The pericardial membranes were smooth and glistening. The right auricle was slightly dilated. The foramen ovale was patent and admitted a thin probe. The tricuspid valve was thin and delicate. The right ventricle was not hypertrophied. The pulmonic valve and artery were normal. The left auricle was slightly dilated; its endocardium was smooth, and the appendage contained no thrombi. The mitral valve was thin and delicate. The left ventricle was slightly dilated but not hypertrophied. The myocardium was about 8 mm. thick, firm and pale gray in color. The aortic valve was thin and delicate. The coronary arteries and ostia were normal. The aorta was moderately elastic and contained an occasional minute atheroma.

Lungs.—The lungs were large and firm and weighed 150 gm. The pleural surfaces were smooth, glistening, and purple-pink in color. There was a small azygos lobe

attached to the right upper lobe. Both lungs were hypocrepitant. On section they showed moist purple-pink surfaces which oozed considerable white fluid. There were several dark red, fleshy, poorly aerated areas in the dependent portions of both lower lobes. The trachea and larger bronchi were filled with frothy fluid. The tracheobronchial and bronchopulmonary lymph nodes were not remarkable.

Liver.—The liver was slightly enlarged and weighed 295 gm. The lower borders were moderately rounded. The capsule was smooth and glistening. Section revealed a light brown surface mottled by irregular yellow areas. The lobular markings were indistinct. The portal vein, hepatic artery, and hepatic vein showed no gross changes. The gall bladder was not enlarged. It was filled with golden-yellow bile. The mucosa had a delicate lacelike structure. The hepatic, cystic, and common ducts were patent. The latter opened into the duodenum at the papilla of Vater.

Spleen.—The spleen was moderately firm and weighed 30 gm. The capsule was smooth and glistening. Section showed a firm reddish-brown pulp speckled by prominent pinhead-sized white follicles. The splenic artery and vein were not remarkable.

Pancreas.—The pancreas was normal in size and shape. On section it presented the usual buff-colored lobulations. The duct of Wirsung was patent and opened into the duodenum at the papilla of Vater.

Adrenals.—The adrenals were similar in size and shape and were normal on section.

Genitourinary Tract.—The kidneys were similar in size and shape and weighed 70 gm. together. The capsules stripped with ease. The surfaces showed a moderate amount of fetal lobulation. Section revealed a swollen moist surface. The cortex was pale yellowish tan and was poorly demarcated from the yellowish pink medulla. The glomeruli were visible as white dots. The right renal pelvis was slightly dilated. The renal arteries and veins showed no significant change. Both ureters were patent and opened into the bladder at the upper angles of the trigone. The bladder was not enlarged. Its mucosa was smooth. The prostate and seminal vesicles were normal. The testes were small and firm. Section showed moist tawny surfaces from which the tubules could be "strung."

Gastrointestinal Tract.—The esophagus, stomach, small intestine, appendix, colon, and rectum showed no significant changes. One noted particularly the absence of a slate gray color.

Thyroid.—The thyroid was normal in size and shape and showed on section a fleshy homogeneous dark red surface.

Bones.—Sections of the lower end of the left femur and upper end of the left tibia revealed a marked widening of the provisional zone of calcification subjacent to the epiphyseal cartilage. This area measured about 4 mm. in width, was pinkish-gray in color, and stony hard. It contrasted sharply with the spongy red marrow of the metaphysis. The costochondral junctions of several ribs from either side showed a similar change, except that the pink-colored, compact, eburnated bone was not quite so sharply demarcated from the adjacent marrow. The epiphyses of the lower left femur and upper left tibia showed a rim of dense petrification about 3 mm. thick lying between the inner core of spongy bone and the outer surrounding hyaline cartilage. In none of the bones was the gray discoloration usually characteristic of lead deposition in bones found.

Brain.—The scalp and calvarium were normal. The dura mater was densely adherent to the calvarium and was removed with the latter. There was marked excess of cerebrospinal fluid in the subarachnoid spaces. The cerebral vessels, especially over the parieto-occipital lobes, were extremely congested. The brain tissue was very soft in consistency and very friable. The meninges over the base of the brain were slightly cloudy.

Microscopic Examination

Mitral Valve.—Slight edema of valve. Group of mesenchymal cells in valve pocket and a few scattered throughout the valve.

Aorta.—Thickening of intima.

Lungs.—Bronchopneumonia. Acute and chronic bronchitis. Congestion. Edema. Focal atelectasis.

Liver.—Congestion. Diffuse fatty changes. No intranuclear inclusion bodies found.

Spleen.—Moderate congestion.

Adrenals.—Hemorrhage into medulla. Macrophages filled with hemosiderin in area of hemorrhage.

Kidneys.—Slight congestion and edema. Slight vacuolar degeneration of tubular epithelium.

Bones.—Costochondral junction showed thickening of area of new bone formation at the junction of the epiphysis with the metaphysis. Fibrosis was seen in the marrow spaces and increased erythropoiesis in the rest of the marrow. Lead stain showed deposition of lead sulfide granules in the spicules of bone at the junction of the epiphysis with the metaphysis. Lower epiphysis of the femur showed the same changes.

Brain.—The leptomeninges were somewhat thickened. The meningeal blood vessels were engorged. The nerve cells of the cortex showed degenerative changes varying from "acute" swelling to "chronic" shrinkage, the latter changes being most common in the outer cortical layers. With silver stains the cytoplasm of some of the nerve cells displayed finely granular material. The glial elements about the nerve cells in the cerebral cortex were increased; the perineural spaces were enlarged. The small blood vessels were uniformly engorged, often showing endothelial proliferation. The perivascular spaces were enlarged and often surrounded by small areas of rarefaction. Some of the perivascular spaces were filled with a clear, eosin-staining substance. About these glial nuclei were crowded in large numbers.

In some areas there were found small extravasations of red blood cells. With special stains perivascular gliosis was readily demonstrated with astrocytes often gathered about blood vessels. Fat preparations (Scharlach red) showed an increased amount of fat in some regions where fat droplets pervaded phagocytic glia. In some areas finely divided fat droplets were found scattered free in the tissue. A lead stain was employed but failed to reveal lead.

Conclusion.—Generalized anemia. Pulmonary edema and congestion. Focal bronchopneumonia. Azygos lobe. Small foramen ovale. Moderate dilatation of all the chambers of the heart. Parenchymatous degeneration of the liver with fatty changes. Distinctly increased density of provisional zones of calcification of ribs, left femur and tibia. Cerebral edema. Diffuse degenerative encephalopathy with disseminated gliosis (lead?). Chemical analysis of 170 gm. of liver yielded 1.5 mg. lead.

The mother was examined for any evidence of lead poisoning. Her blood showed the following: hemoglobin, 73 per cent (Sahli); red blood cells, 3,760,000; color index, 0.97; white cells, 5,800; polymorphonuclear leucocytes, 61 per cent; lymphocytes, 34 per cent; monocytes, 2 per cent; eosinophiles, 3 per cent; no basophilic stippling.

One week after discontinuing the use of the nipple shields the mother's urine was examined and found to be negative for lead. At the same time, that is, after she had discontinued nursing for a week, the milk remaining in the breasts was expressed and found to contain 0.05 mg. of lead per 100 c.c. The mother had experienced no colic and had no neurologic complaints. There was no evidence of a lead line on her gums.

Wilcox and Caffey[6] in 1926 were the first to call attention to lead nipple shields as the cause of infantile lead poisoning. They reported the cases of two infants, aged respectively 4½ and 9 months, both of whom suffered from lead encephalopathy resulting from the use of lead nipple shields. Both these infants recovered.

Findlay[7] in 1935 reported the case of an infant, aged 3½ months, treated for poor nutrition and anemia. The case was first diagnosed as von Jaksch's anemia, but the large number of stippled cells in the blood led to the diagnosis of lead poisoning. "On enquiring of the mother of any possible source of lead, it was learned that, owing to sore nipples, she had all the time the child was at the breast protected them by the use of leaden shields (Dr. Wansborough's metallic shields). These were applied between the feedings, and neither the nipples nor the shields (which on inspection were found to be corroded) were ever washed."[7] The child died of pneumonia. No autopsy was obtained.

The fact that lead nipple shields may be purchased without doctor's orders and that they are routinely prescribed by many physicians and used as a routine procedure in many hospitals led us to inquire among pediatricians as to the frequency of lead poisoning from this particular source. Dr. Charles F. McKhann, who has published numerous articles on lead poisoning, replied that he had seen three such cases and put the following note at our disposal:

Patricia D., 6 months old. The chief complaint was vomiting and convulsions. One week before entry she started projectile vomiting during feedings. Lead nipple shields were worn by the mother. Two days before entry there was a clonic convulsion lasting one hour.

Daily urinalyses showed many white blood cells and slight traces of sugar. Blood studies showed about 10 per cent stippled cells. X-rays showed a zone of increased density at end of long bones and ribs, suggestive of "lead line."

Diagnosis: Lead encephalitis.

Dr. Stewart H. Clifford of Brookline, Mass., kindly allowed us to include the case history of an infant observed by him. His description follows:

"Lillian S., born March 3, 1934. Family history, negative. Full term, normal delivery at the Boston City Hospital. Condition good at birth; no resuscitation needed. Neonatal course uneventful. Completely breast fed. Birth weight, 6 pounds and 14 ounces. General condition excellent until July 7, 1934, when she began to vomit without fever or other signs of an infection. She vomited several times during the day and that night had a convulsion involving the right side of the face and body, lasting 45 minutes. Ten minutes later another convulsion began, involving the left side of the body and lasting 10 minutes.

"At this time I was called for the first time and advised hospital admission. A complete physical examination was negative, revealing a normal, well nourished, breast-fed baby weighing 12 pounds and 12 ounces. The temperature and blood count were normal. In the face of the negative findings, the story was investigated for a history of lead.

"The mother had had sore nipples in the hospital for a few days, and nipple shields were used with relief. On arriving at home, the nipples again became sore, and remembering the hospital treatment, she purchased lead nipple shields and wore them continuously up to admission. Before each feeding the nipple shield would be removed and the breast washed with boric acid solution; after the nursing the process was reversed.

"Because of this history, an emergency x-ray picture of the long bones was taken, revealing the typical wide bands of lead poisoning.

"The red blood count was 4,000,000; the white count, 15,000. The smear showed 40 per cent polymorphonuclears, 55 per cent lymphocytes, and 5 per cent monocytes, with from 4 to 18 per cent stippled cells at various determinations.

"The baby was kept in the hospital; the course was normal with no more convulsions. She was sent home and was to be given large doses of viosterol and calcium lactate.

"On July 12 she vomited and went into a convulsion lasting one and one-half hours, at which time she was brought to my office, and the convulsion was terminated by anesthesia with ethyl chloride.

"About eight hours later another convulsion occurred, and the child was readmitted to the private ward. The convulsion was relieved by magnesium sulfate.

"July 16 another attack of convulsions began, and for reasons of economy the patient was admitted to the public ward. The physical examination was negative; the blood pressure, fontanel, and eye grounds were reported as negative. The spinal fluid pressure with the infant crying was 300 mm. of water. The fluid was clear in color, with a positive Pandy reaction, normal sugar, fifteen cells of the monocyte series, and a total protein of 180 mg. per cent. Tuberculin and Wassermann tests were negative.

"For the next eighteen months the infant was seen at frequent intervals and found to be developing normally.

"On Dec. 17, 1935, she was brought to the office with temperature of 102° F. and a convulsion. Physical examination was negative except for injected and swollen tonsils. She was admitted to hospital where the temperature fell to normal in twenty-four hours. There were no more convulsions. Hemoglobin was 85 per cent, red cells 5,560,000, white cells 13,000. No stippled cells were found in the blood smear.

"From this time until June, 1937, the child was seen at infrequent intervals and found to be developing physically and mentally in a normal manner.

"Diagnosis: lead poisoning, lead encephalitis."

Personal communication with Dr. John Caffey, coauthor of the original article on lead poisoning from nipple shields, revealed that since the report of the original two cases, several other similar cases had been observed at the Babies Hospital in New York City.

Of the six cases of lead poisoning due to nipple shields which we have been able to collect, six showed evidence of brain involvement, convulsions being the most striking symptom. Our own patient presented the perfectly characteristic findings of severe lead encephalopathy.[5]

It appears that the lead nipple shield is a definite source of danger to the nursing infant. In spite of this, the lead nipple shield is commonly employed and highly recommended in the treatment of fissured

nipples. It can be purchased at almost any drugstore.* The descriptive matter accompanying these shields states that they have been used since 1842 and that "they are in no way likely to be injurious to the infant." Obstetricians[8] who recommend these nipple shields feel that, with careful washing of the nipples with a boric acid solution, there is no possible danger to be encountered.

A very recent pertinent correspondence was reported in the *British Medical Journal*[9] in which a chemist questions the possible harmful effect of the use of lead nipple shields. In response, a physician (Dr. Walker) states that "the danger is very remote, and I have neither heard of nor read of any case having been observed." As stated above, in our own case a specimen of breast milk, obtained one week after nursing had been discontinued, contained a large amount of lead. We see, therefore, that not only is lead present in the milk when in contact with the shield as pointed out by Savage,[9] who states, "I can confirm from experiment that lead is to be found in milk left in contact with the shields," but it may also be found some days after their removal from the breast. It seems probable that the lead penetrates into the deeper layers of the skin and into the ampullae of the breast, thus contaminating the milk as it is being excreted.

It is of interest that cases of poisoning from lead nipple shields are not encountered or reported more often, especially when one considers the frequency with which lead shields are used. The rarity of frank cases of intoxication may be due to the fact that there is a well-known personal variation of susceptibility to lead, as well as the fact that most mothers stop using the shields after a few weeks. In the reported cases, the shields were used for months, in one case for six months. However, there are undoubtedly many infants who must absorb toxic amounts of lead even when the shields are used for only a short period of time. These children need not necessarily show recognizable clinical signs of poisoning.

Undoubtedly many cases of unexplained anemia, colic, or convulsions occurring later in infancy may be due to lead in the body. This is all the more likely since we know that in lead poisoning symptoms need not make their appearance till years after the entrance of lead. Thus Blackman[5] cites the case of a child in which three years elapsed between the original convulsions and the final attack of lead encephalopathy. It is this latter fact that we wish to emphasize. It is well-known that among adults, lead intoxication masquerades under the guise of many other illnesses; witness the recent extraordinary report of Dr. Horatio Williams.[10] We believe that the same must hold true of infants as well.

*Since the post-mortem report of our patient, the New York State Department of Health has issued a regulation prohibiting the sale or use of lead nipple shields within the state.

SUMMARY AND CONCLUSIONS

A fatal case of lead poisoning in a 4-month-old nursing infant, due to the use of lead nipple shields, is reported.

Two previously undescribed non-fatal cases are reported.

The literature is reviewed, and the danger of the use of lead nipple shields is emphasized.

Lead nipple shields are fraught with definite danger to the nursing infant, and their sale should be prohibited.

NOTE.—Since this paper was submitted for publication, another case has appeared in the literature: Rapoport, Milton, and Kenney, Athol S.: A Case of Lead Encephalopathy in a Breast-Fed Infant, Due to the Use of Lead Nipple Shields by the Mother, J. A. M. A. **112**: 2040, 1939.

REFERENCES

1. Ganiayre, R.: Thèse de Paris, 1900.
   Legrand and Winter: quoted by Dufour-Labastide, Thèse de Paris, 1902.
2. Holt, L. E., Jr.: Am. J. Dis. Child. **25**: 229, 1923.
   Norton, N. R.: Internat. Clin. **4**: 231, 1922.
3. Kato, K.: Am. J. Dis. Child. **44**: 569, 1932.
4. Williams, H., et al.: J. A. M. A. **100**: 1485, 1933.
5. Blackman, S. S., Jr.: Bull. Johns Hopkins Hosp. **61**: 1, 1937.
6. Wilcox, H. B., and Caffey, J. P.: J. A. M. A. **86**: 1514, 1926.
7. Findlay, Leonard: Post-Grad. M. J. **11**: 251, 1935.
8. Mount, W. B.: Internat. Clin. **2**: 206, 1937.
   Emmert, F.: J. Missouri M. A. **30**: 155, 1933.
9. Savage, R. Maxwell: Brit. M. J. **1**: 198, 1939.
   Walker, J.: Brit. M. J. **1**: 312, 1939.
10. Williams, Horatio: J. A. M. A. **112**: 534, 1939.

1097 PARK AVENUE

RITTER'S DISEASE

Review of Literature With Report of a Case

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SIXTY years ago Ritter von Rittershain[1] published the description of a peculiar exfoliative dermatitis of newborn infants, since known by his name. The description was based on his observations of 297 infants over a ten-year period, during which time he was physician to an orphan asylum in Prague.

Ritter's disease, or dermatitis exfoliativa neonatorum, according to Ritter and subsequent authors, occurs in newborn babies usually in the second week of life; the onset is characterized by slight redness of the skin around the corners of the mouth, which quickly spreads to the rest of the face, body, and extremities. Large portions of the epidermis become wrinkled, being detached from the dermis, and are either pulled off or shed spontaneously. Such desquamation may be so marked that casts of the extremities may be pulled off in the form of a glove or sock. The surface exposed by the desquamation is reddened and dry, no serous discharge being present; it has the appearance of a scald. Symptoms of constitutional origin are rarely present; there usually is no weight loss, no fever, nor diarrhea. In those patients who survive, seven to ten days elapse before recovery is complete; the desquamation gradually ceases, and the skin takes on a normal appearance. About 50 per cent of the infants die, death occurring within the first few days of the disease.

CASE REPORT

A white female infant, A. W., was admitted to the pediatric ward on July 15, 1938, because of jaundice and the vomiting of blood. The child, who weighed 8½ pounds at birth, had been born at home spontaneously after an eleven-hour labor. During the first day of life the child had nursed well every three hours but had refused the night feedings. On the second day, she had begun to regurgitate dark brown material about one hour after feedings. Although the child had continued to nurse well, the regurgitation became progressively worse, and, in addition, she had begun to cry out with paroxysms of abdominal pain. The evening before admission the child had vomited everything taken by mouth.

The family history disclosed the fact that the father and several others in his family suffered with duodenal ulcers. There were four other children in the family, all living and well. The mother suffered two miscarriages during 1937; on each occasion the pregnancy had progressed three months. The blood Wassermann reaction of both mother and father was negative.

The examination on admission revealed a markedly dehydrated infant, weighing 6 pounds and 4 ounces; the temperature was 99.6° F.; the skin was dry and icteric; the fontanels sunken; a brownish discharge was found in the nares and

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pharynx; the lungs were clear; the heart was slightly enlarged to the left, and a localized systolic murmur was heard at the fourth interspace to the left of the sternum; the liver was felt two fingerbreadths below the costal cage; the spleen was not palpable; the neurologic examination revealed no abnormalities.

The temperature remained within normal limits during the first two days of hospitalization; on the third day, it rose to 102° F. but fell immediately to normal, where it remained until death, except on the fifth day when it was elevated to 100.6° F. on one occasion. Death occurred on the morning of the sixth day of hospitalization.

On admission the child was given a 3-ounce feeding of a lactic acid formula. She frequently vomited brownish material which gave a positive test for occult blood. Fluoroscopic examination showed the stomach to be markedly dilated. An x-ray study of the upper intestinal tract revealed that no barium had passed through the pylorus at the end of two hours. At the end of 24 hours most of the barium was still in the stomach though a small amount had passed into the small intestine. The child refused the bottle, and gavage feedings were resorted to. The return flow of fluid resulting from gastric lavage which preceded each feeding was brownish red in color. On the third day of hospitalization, examination revealed a cylindrical mass in the left upper abdomen extending across the midline to the level of the umbilicus. At its lower part there seemed to be a narrow cordlike process which changed in character, first appearing to be a few millimeters in diameter, later increasing to 1.5 cm. in diameter. The physical signs suggested pyloric or duodenal stenosis, and for this reason the child was given 0.001 gr. atropine sulfate fifteen minutes preceding each feeding for five doses. No reaction to the drug was noticed. On the following morning at 6 o'clock the upper part of the back was found to be red. Two hours later the area of redness had spread over the entire back, and small erythematous areas had appeared around the eyes, mouth, and ears. By noon, these erythematous lesions had spread so that they were widely distributed over the face, chest, abdomen, and back. They were circumscribed and discrete but rapidly became confluent so that the skin looked as if it had been scalded. By this time the earliest lesions showed extensive exfoliation, the loose epidermis being easily rubbed off with the slightest touch. This process continued until the trunk and face were denuded. Death occurred 25 hours after the first sign.

Examination of the blood on admission showed 19 gm. of hemoglobin, 6,140,000 red blood cells, a color index of 0.72; 22,300 leucocytes with 83 polymorphonuclears, 9 lymphocytes, and 7 monocytes. There were 6 nonfilamented cells and 1 premyelocyte; there was anisocytosis; and one nucleated red blood cell was seen. The vomitus was slightly alkaline in reaction, was negative for bile, and contained numerous bacteria, both gram-negative bacilli and gram-positive cocci, red blood cells, a few yeast cells, and an occasional pus cell. A stool examination was strongly positive for occult blood, was negative for starch, and showed an occasional fat globule, a moderate number of calcium soaps, and a few hematoidin crystals. A culture taken from beneath the shedding epidermis revealed a virulent type of hemolytic *Staphylococcus aureus*. Blood culture taken at autopsy, three hours after death, was overgrown with *Bacillus proteus* which was most probably a contaminant.

Pathology.—At autopsy the body presented a striking appearance (Figs. 1 and 2). Almost the entire skin surface of the face, trunk, and extremities showed an exfoliating dermatitis. The superficial layers of the skin were torn and hung loose in large sheets. The skin of one of the lower extremities was pulled off intact, resulting in a stockinglike cast of the foot, leg, and thigh. Over the buttocks and abdomen the underlying skin was red, moist, and glistening, having

the appearance of a severe second degree scald. Over the legs the underlying skin was white and smooth. The mucous membranes of the mouth, pharynx, and vagina did not share in this exfoliating process.

The stomach and first portion of the duodenum were markedly dilated. The second portion of the duodenum showed an almost complete atresia at the point where the ampulla of Vater should be found, the lumen barely admitting a wire probe. The ampulla could not be found, and, although the gall bladder contained a small amount of bile, it could not be expressed through the common bile duct. There was bile staining of the stomach contents as well as the contents of the ileum below the narrowed lumen. The atresia appeared to be congenital in origin.

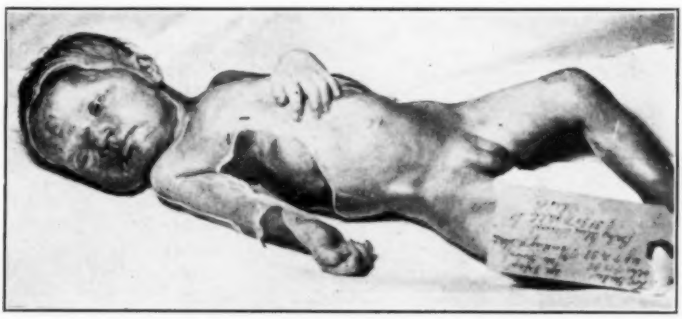

Fig. 1.—Photograph immediately after death showing complete desquamation of the face and portions of the body.

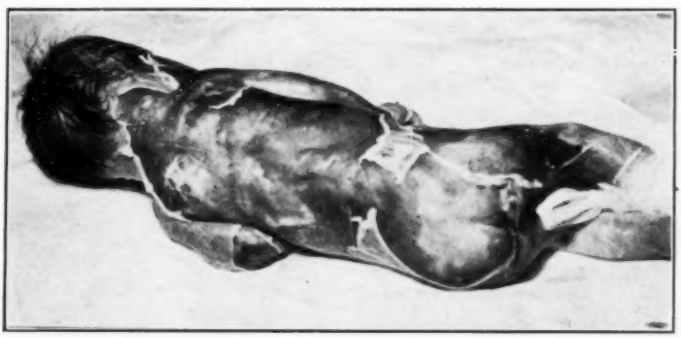

Fig. 2.—Photograph immediately after death. The superficial layers of the epidermis hang in loose sheets and shreds. The underlying skin has a red, scalded appearance.

In addition to being dilated, the stomach had a definitely thickened wall. Almost the entire mucosal surface was involved with an extensive ulcerative process. The largest of these ulcers extended from the fundus to the pylorus along the greater curvature. The edges were thick and had a rolled appearance; the floor was composed of red, necrotic tissue. Other ulcers were situated over the surface so that approximately 50 per cent of the mucosa had sloughed away, leaving small isolated patches of thickened mucosa. The first portion of the duodenum was dilated; the wall was thin, but the mucosa was normal in appearance. The pharynx, esophagus, and the gastrointestinal tract distal to the constricted portion

of the duodenum were normal. There were petechial hemorrhages in the epicardium. There were small areas of hemorrhage about 3 mm. in diameter throughout both lungs and visceral pleura. The parenchyma of the liver had a fatty appearance.

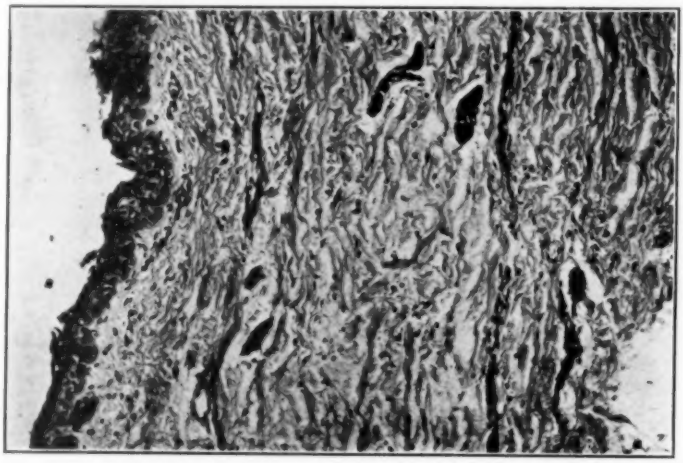

Fig. 3.—Microphotograph of the epidermis and corium. The superficial layers of the epidermis have sloughed away. The corium is edematous but shows little evidence of an inflammatory reaction.

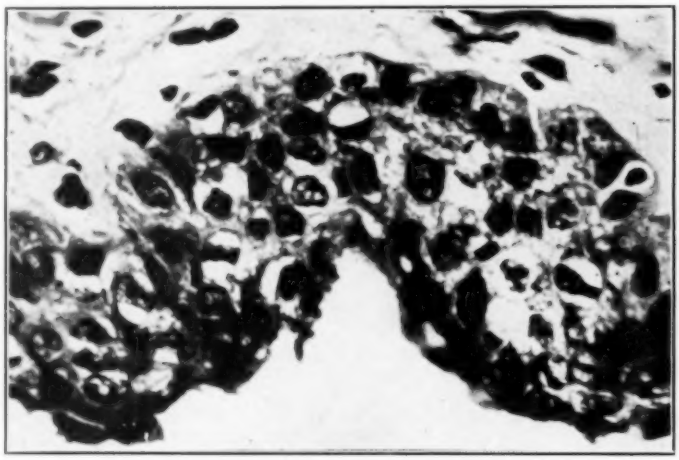

Fig. 4.—A microphotograph of the epidermis. Note the degenerative changes in all the cells, most evident along the outer surface left by the sloughing of the strata corneum and lucidum.

The microscopic picture of the skin is shown in Figs. 3 and 4. Most of the cells of the granular layer had apparently sloughed with the stratum lucidum and corneum. The few remaining cells on the surface showed far advanced degenerative changes. The germinal layer was abnormally thin, averaging three to

five cell layers, whereas in the normal there are usually more than five. The layer of basal cells of the epidermis was irregular and rather poorly differentiated from the cells of the corium, especially at the tips of the papillae. Definite degenerative changes were detectable in these layers. The cells were frequently separated by what appeared to be fluid; the cytoplasm contained large irregular vacuoles; the nuclei showed chromolysis and poor staining quality. There was perhaps a paucity of sebaceous glands in the corium. At no point were collections of inflammatory cells seen, nor were bacteria obvious. The process appeared to be one of degeneration and edema, beginning at the basal layer and progressing through the outward layers to cause a splitting of the stratum granulosum with loss of the keratinized cells.

The pathologic changes of the gastric mucosa and submucosa were those of inflammation. Where the mucosa was present between the ulcers, it was well preserved. The ulcerative process had extended through the submucosa into the muscularis, where the tissues were necrotic with complete loss of cell detail. In these areas there were large collections of leucocytes and masses of gram-positive cocci and gram-negative bacilli.

The remaining pathology of importance was an acute inflammatory and degenerative process in the thymus, a rather severe myocardosis, fatty metamorphosis of the liver, and small hemorrhages in the lungs.

DISCUSSION

The etiology of dermatitis exfoliativa neonatorum is a much discussed question. Ritter, in his original article, considered it a "pyemia occurring in epidemic form." He believed it to be noncontagious. In 1898 Winternitz[2] postulated four possible causes: (1) local infection, (2) irritation of the central vasomotor apparatus resulting in a vasomotor disturbance, (3) an increase in the normal physiologic desquamation, and (4) a nutritional disturbance of the vascular layer of the epidermis.

Since then, however, there have been numerous reports[3] of dermatitis exfoliativa neonatorum occurring in children who have been exposed to pemphigus. However, from the description, some of these cases were probably true pemphigus. Most writers[4] agree that this disease is a variety of pemphigus, varying only in the degree of severity. Apparently the disease is not contagious since no epidemics have been reported. Wirz,[5] however, reports the case of an infant who was delivered in a foundling asylum and later transferred to a hospital where he developed Ritter's disease. No other cases of Ritter's disease or pemphigus were known in these institutions; however, several other children in both of these institutions later developed pemphigus. Various organisms such as *Staphylococcus albus*, *Staphylococcus aureus*, and streptococci have been recovered from the skin of children suffering with Ritter's disease. We were able to culture *Staphylococcus aureus* from beneath the exfoliating epidermis which was still attached to the skin. However, against bacterial infection as the cause of Ritter's disease is the fact that the histologic picture is noninflamma-

tory. McCarthy[6] explains the variance in the clinical manifestations and pathologic picture from what is usually seen in impetigo and pemphigus on the basis of the "biologic peculiarity of the skin of the newborn." This hardly seems an adequate explanation.

Skinner[7] has suggested that a diffuse peripheral vascular lesion is the cause of Ritter's disease. In our case, at no point could even the smallest vessel be shown to demonstrate any peculiarity. Since the disease always develops in the first few weeks of life and since the skin lesion appears to be a rapid degenerative process, a congenital inadequacy of the blood supply to the skin seems reasonable. It is extremely difficult to estimate from microscopic sections just how many vessels are necessary to nourish the skin adequately and whether in Ritter's disease the number present is insufficient.

Avitaminosis should also be mentioned as an etiologic possibility. The fact that this child had an ulcerative gastritis and an almost complete high intestinal obstruction might mean a total inability to utilize vitamins taken by mouth. But this disease occurs so early in life that we would have to assume the avitaminosis to be congenital in origin. This can probably be excluded in our case since there were no manifestations of vitamin deficiency in the mother, and her diet appeared to be adequate.

Acute ulcerative gastritis in the newborn is rare. In our case the child began to vomit blood during the first day of life; thus it must be assumed that the ulcerative gastritis was congenital or developed in the first twenty-four hours after birth. It is difficult to explain the relation of the lesions in the gastric mucosa to those in the skin. Guy and Cohen[8] reported a case of Ritter's disease associated with ulcers in the jejunum. This is the only other report where exfoliation of the skin and ulceration of the alimentary tract were simultaneously seen. If we assume the etiology of the skin lesion to be a congenital defect in the nutritive layers of the epidermis or in the vascular supply to the skin, we might offer a similar explanation for the changes seen in the gastrointestinal tract. It is true that acute ulcerative gastritis is occasionally seen secondary to a septicemia and acute toxic states, but in Ritter's disease the blood stream is usually sterile and a lack of the symptoms of toxicity is notable. Our patient also had congenital duodenal atresia. It is perhaps more plausible to associate the ulcerative gastritis with this abnormality of the gastrointestinal tract, although the literature gives few examples, than to associate the gastrointestinal lesions with the exfoliative dermatitis, since in the first place, the pathologic changes in the two are absolutely different, and, in the second place, in the large number of cases of Ritter's disease reported such an association has only occurred once before.

The cause of death in Ritter's disease has never been adequately explained. In our case death was seemingly the result of starvation due to the ulcerative gastritis and the stenosed duodenum. In uncomplicated Ritter's disease it seems reasonable to assume that death is the result of the loss of function of the skin, although it is not obvious from the literature that death or recovery has been correlated with the extent of exfoliation.

In conclusion, we must assume that the cause of Ritter's disease is still unknown. This being true, no prophylactic measures can be described, and no system of therapy, other than general supportive treatment, can be recommended.

REFERENCES

1. Ritter von Rittershain: Centralzeit. f. Kinderh. **1**: 3, 1879.
2. Winternitz, R.: Arch. f. Dermat. u. Syph. **44**: 398, 1898.
3. a. Hedinger, E.: Arch. f. Dermat. u. Syph. **80**: 349, 1906.
   b. Brown, W. M.: J. A. M. A. **49**: 1670, 1907.
   c. Foster, B.: J. Cutan. Dis. **25**: 164, 1907.
   d. Fisher, J. E., and Wittenberg, S. S.: Arch. Dermat. & Syph. **10**: 289, 1924.
   e. Zakon, S. J.: Arch. Dermat. & Syph. **24**: 830, 1931.
4. a. Hedinger, E.: Ibid.
   b. Stellwagon, H. W.: Diseases of the Skin, Philadelphia, 1921, W. B. Saunders Co., p. 198.
   c. Haldin-Davis, H. D.: Brit. J. Dermat. **39**: 435, 1927.
   d. Van Vanno, N. C.: Nederl. tijdschr. v. geneesk. Abst. Am. J. Dis. Child. **43**: 217, 1932.
   e. Gate, J., Ciuleret, P., and Chapius, A.: Nourrisson **22**: 293, 1934.
   f. Boisson, G.: Nourrisson **23**: 28, 1935.
   g. Daveo and Bassargette: Nourrisson **23**: 238, 1935.
   h. Neff, F.: Arch. Pediat. **51**: 465, 1934.
5. Wirz, B.: Cor.-Bl. f. schweiz. Aerzte. Abst. J. A. M. A. **68**: 230, 1917.
6. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, 1931, The C. V. Mosby Co., p. 145.
7. Skinner, F.: Brit. Med. J. **22**: 75, 1910.
8. Guy, W. H., and Cohen, M.: Arch. Dermat. & Syph. **19**: 425, 1929.

LEUKEMOID REACTION WITH SULFAPYRIDINE

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IT IS our feeling that physicians should be informed of new and unexpected reactions occurring with the use of sulfapyridine. With this thought in mind, the following case of an unusual leukemoid reaction is reported.

History.—J. O., a Mexican boy 9 years of age, entered the hospital the evening of March 17, 1939, complaining of sore throat, headache, nonproductive cough, and pain in the upper right chest during the preceding twenty-four hours. The mother stated that there had been fever for this same period although the temperature had not been taken. Family history was without significance, as was the child's past history.

Examination.—Physical examination revealed an extremely toxic child with temperature of 103.8° F., pulse 140, and respirations numbering 40 to 50 per minute. Pharynx was moderately injected, and there was some purulent discharge in nose. Chest findings were those of a right upper lobe consolidation.

Laboratory.—On entry the urine was negative, and the blood picture was as follows: hemoglobin 70 per cent (Sahli); red blood cells, 3,250,000; white blood cells, 24,280 (neutrophiles 92 per cent, lymphocytes 8 per cent). Laryngeal swab produced Type I pneumococcus. Blood culture showed growth in twenty-four hours for Type I pneumococcus. X-ray pictures of chest revealed consolidation of the right upper lobe with left lung field and remainder of right lung clear.

Course and Treatment.—Inasmuch as this particular case was one of our sulfapyridine series, nothing else was used except oxygen and such other general care as was deemed necessary for the comfort of the patient. Sulfapyridine was started on March 20, three days after onset of symptoms, with an initial dose of 1.5 gm. Subsequently he received 1 gm. every 4 hours until March 23. Total amount of drug given during this three-day period was 13.5 gm. It is to be noted that twenty-four hours after the first dose (6.5 gm. of the drug during the twenty-four-hour period) the temperature dropped from 104.4° F. to normal, pulse from 140 to 110, and respirations from 50 to 30. On March 24 (twenty-four hours after drug discontinued) and again on March 25, the temperature rose to 102° F. (Chart 1). It was during this febrile period that onset of the marked blood changes was observed.

Blood concentration of sulfapyridine was determined at the end of twenty-four hours and found to be 10 mg. per 100 c.c. of blood. It was again determined six hours after the last dose was given and found to be 5 mg. Twenty-four hours after stopping the drug, the concentration was 2.7 mg.

On the day the drug was stopped (March 23), the patient was asymptomatic and appeared well, and chest examination, both clinical and roentgenologic, showed almost complete resolution. On this day the blood count showed no great change from that on entry with the exception of the white blood count. The blood picture was hemoglobin 60 per cent, red blood cells, 3,240,000, white blood cells, 14,700 (84 per cent neutrophiles, 16 per cent lymphocytes).

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On March 24, twenty-four hours after stopping the drug, with the temperature rise to 102° F., the clinical picture changed. The patient refused to eat, there was marked pallor of the skin, and the sclera showed a slight icteric tinge. Blood examination revealed an icteric index of 22, hemoglobin 25 per cent, red blood cells, 1,380,000, white blood cells, 58,600 (66 per cent neutrophiles, 14 per cent lymphocytes, 2 per cent monocytes, 0.5 per cent eosinophiles, 9.5 per cent myelocytes, 1.5 per cent promyelocytes, 5 per cent metamyelocytes, 1.5 per cent plasma cells). Morphologically the red blood cells showed macrocytosis, poikilocytosis, 42 normoblasts, 3 megaloblasts, and 11 macronormoblasts per 200 white blood cells. An emergency transfusion of 150 c.c. of citrated, Type IV blood was given at 3 P.M.

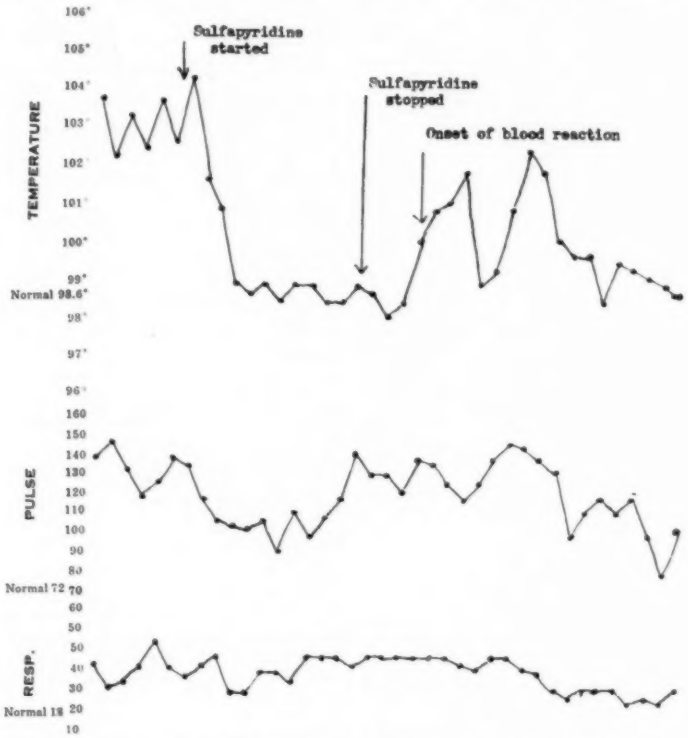

Chart 1.—J. O. Graph showing temperature, pulse, and respiration.

At 6 P.M. the patient complained of pain in both costovertebral angles. The next urine passed (100 c.c.) was port wine in color and showed a positive test for occult blood; however, no red blood cells were seen microscopically. No discoloration of the urine had been noted previously. The red color persisted for two days but no red cells were ever present. A few leucocytes and finely granular casts were noted for five or six days. The daily blood counts are recorded in Table I.

On March 29, a diagnostic sternal puncture was done. The bone marrow showed nothing indicative of leukemia. There was moderate hyperplasia. Two subsequent blood transfusions of 150 c.c. each were given without reaction. Enteric medication was offered in the form of copperin B and iron ammonium citrate. Liver extract

was injected every third day. After the precipitous drop of the white cells (see Table I) yellow bone marrow extract was given three times daily for seven days.

TABLE I

DAILY BLOOD COUNTS

DATE	% HB	RED BLOOD CELLS		WHITE BLOOD CELLS						
		COUNT	APPEARANCE	COUNT	DIFFERENTIAL*					PERCENTAGE OF IMMATURE CELLS
					P	L	M	E	B	
3/18/39	70	3.25	Normal	24,280	92	8				
3/22/39	60	3.24	Normal	14,700	84	16				
3/24/39	25	1.38	Macrocytosis Normoblasts —42 Megaloblasts —3 Macronormoblasts—11	58,600	66	14	2	5		Myelocytes 9.5 Promyelocytes 1.5 Metamyelocytes 5.0 Plasma cells 1.5
3/25/39	25	1.39	Macrocytosis	61,500	80	11	9			
3/26/39	23	1.29	Macrocytosis	81,200	82	7	11			
3/27/39	25	1.40	Macrocytosis	75,600	63	12	1	1		Myelocytes 9.5 Promyelocytes 1.0 Myeloblasts 0.5 Metamyelocytes 12.0
3/28/39	30	1.51	Macrocytosis	34,300	75	15	10			
3/29/39	45	2.06	Macrocytosis	17,500	64	20	16			
3/30/39	47	2.08	Macrocytosis	10,700	86	17	7			
3/31/39	53	2.75	Macrocytosis	8,100	56	30	14			
4/ 4/39	66	2.63		4,400	42	57				
4/ 6/39	72	3.91		6,550	42	50	5	1	1	
4/26/39	84	4.22		7,500	38	48	6	6	2	

*P, polymorphonuclears; L, lymphocytes; M, monocytes; E, eosinophiles; B, basophiles.

On April 14, twenty-seven days after admission and twenty days after onset of blood changes, the patient was discharged as clinically well. A checkup in two weeks revealed him completely recovered. The blood picture at this time showed hemoglobin 84 per cent, red blood cells, 4,220,000; white blood cells, 7,500 (37 per cent neutrophiles, 47.5 per cent lymphocytes, 6.5 per cent monocytes, 6.5 per cent eosinophiles, 2.5 per cent basophiles).

News and Notes

The next regional meetings of the **American Academy of Pediatrics** will be as follows:

Region I, at the Mayflower Hotel, Washington, D. C., April 4, 5 and 6, 1940.

Region II, at the Edgewater Gulf Hotel, Edgewater, Miss., March 22 and 23, 1940.

Region III, at Kansas City, Mo., May, 1940.

Region IV, at Seattle, Wash., May 30 and June 1, 1940.

The **American Pediatric Society** at its annual meeting at Skytop, Pa., elected the following officers for the ensuing year, 1939-40: Dr. Herbert B. Wilcox, New York, president; Dr. Frank C. Neff, Kansas City, Mo., vice-president; Dr. Heyworth N. Sanford, Chicago, recorder-editor; Dr. Hugh McCulloch, St. Louis, secretary-treasurer. The fifty-second annual meeting of the Society will be held also at Skytop Lodge, Skytop, Pa., on May 2, 3 and 4, 1940.

The **Society for Pediatric Research,** at its meeting at Skytop, Pa., elected the following officers: Dr. Daniel C. Darrow, New Haven, Conn., president; and Dr. Mitchell I. Rubin, Philadelphia, secretary.

The Michigan state organization of the **American Academy of Pediatrics,** cooperating with the Preventive Medicine Committee of the state medical society and the Michigan Department of Health, has issued a small booklet on immunization and diagnostic procedures for widespread distribution to the medical profession. This is similar to, but shorter than, the report recently issued by the Academy Committee on immunization procedures. The booklet is published by the Michigan Department of Health and has the approval of the three sponsoring organizations.

As the Journal was going to press, word was received of the death, on October 16, of Dr. Henry Dietrich of Los Angeles, president of the Academy of Pediatrics during 1936.

Dr. Howard B. Hamilton, Omaha, Neb., died on October 12 of coronary thrombosis at the age of 64 years. He was Professor Emeritus of Pediatrics at the University of Nebraska.

Directory of Medical Specialists

The Advisory Board for Medical Specialties will issue in December the first edition of the *Directory of Medical Specialists* listing over 14,000 specialists certified by the twelve American boards and the two affiliate boards in the specialties.

The Directory will have three sections. The first will be devoted to a brief discussion of the Advisory Board for Medical Specialties, its organization and objec-

tives. The second section will have fourteen separate divisions, one for each American board with a geographic and a detailed biographic listing of its diplomates. Each of these divisions will give full information regarding requirements for admission to examinations for certification, details of organization of each board, and other general information. The third and final section will be a complete alphabetical list of all 14,000 diplomates, with their addresses and indications of specialty certification.

It is expected to issue the Directory every two years. No charge is made for any listing in the Directory, and only the names of the specialists certified by the American boards will be included.

Financial support has been given the Directory by the American boards; the project is not designed to be profit-making, and the widest possible public distribution of the Directory is desired. For these reasons the subscription price of the book has been set at a sum ($3.50 per copy) computed to cover only publication expenses.

The Directory will be sold generally to physicians, libraries, hospitals, and others by subscription. Such subscriptions may be made through the Columbia University Press, 2960 Broadway, New York, N. Y.

The American Board of Pediatrics wishes to urge that diplomates of this Board and others interested in pediatrics give their active support by subscribing to the Directory. This is direct support of the work of this Board, as well as of the other American boards, as the Directory will be not only another strong instrument in the improvement of the standards of special medical practice in this country, but also constantly useful for reference in the office of any physician or hospital.